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THIRD SERIES FOUNDED BY EDWARD JACKSON

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DEPARTMENTS

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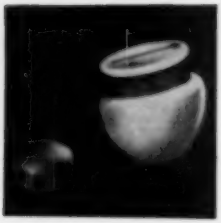

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AMERICAN JOURNAL OF OPHTHALMOLOGY

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AMERICAN JOURNAL OF OPHTHALMOLOGY

VOLUME 33 MARCH, 1950 NUMBER 3, PART I

SARCOIDOSIS OF THE ORBIT*

MARTIN BODIAN, M.D., AND MORTIMER A. LASKY, M.D.
Brooklyn, New York

Sarcoidosis is a chronic disease of unknown origin and relatively benign prognosis characterized by a widespread but variable distribution of a specific granulation tissue. Although its presence has been mentioned and described in many parts of the body, including the various structures of the eye, it has only once been indicated as being present as a separate lesion in the orbit.† The purpose of this paper is to review some of the outstanding facts concerning sarcoidosis and to present a case of this disease with orbital involvement.

Sarcoidosis was apparently first described by Hutchinson in 1875 after observing the ailment for six years.[1] Calling the condition "Mortimer's malady," he bestowed upon his patient's name a dubious and probably unwanted honor. Several years later he wrote another paper in which a second case was presented.[2]

In 1889 Besnier,[3] apparently unaware of Hutchinson's observations, described what is believed by some modern authors[4] to be sarcoidosis. His name for the ailment was lupus pernio. Tenneson[5] added to the subject in 1892 using Besnier's nomenclature.

The term "sarcoid" was originated by Boeck,[6] a dermatologist of Norway, in 1899, who described the skin lesions associated with the disease. Apparently he was unaware at the time that the cutaneous disorder was part of a systemic condition. It was not until 1914 that Schaumann[7] indicated the disease to be a generalized disorder rather than limited to the skin. Reports since then[8] confirming Schaumann's thesis have indicated that the disease is not the great rarity it was once considered.

Levitt[9] compiled a comprehensive review of the literature up to 1941 in which this fact is amply demonstrated. In 1944, Woods and Guyton[4] showed the relation of this disease to uveitis. A good historical account of sarcoidosis was compiled by Hunter in 1936.[10] A recent article by Michelson[11] critically reviewed the possible etiology of sarcoidosis. Although tuberculosis has for a long time been considered as a possible causative agent, pathologic as well as clinical data contradict this theory.

Recently, there has been a fairly general acceptance of the name "sarcoidosis" for the condition under discussion. The next most acceptable name would seem to be "Boeck's sarcoid." Other names have been "benign lymphogranulomatosis," "Besnier's disease," "Schaumann's disease," "Besnier-Boeck-Schaumann's disease," "Noncaseating tuberculosis," "Paratuberculosis," "lupus pernio," "benignes miliar lupoid (Boeck)," "Hutchinson-Boeck's disease," and probably others. And, of course, we must not forget "Mortimer's malady." The *Cumulative Quarterly Index Medicus* uses the term "sarcoidosis" when referring to this disease. Michelson[11] gives pertinent reasons for the use of this term.

* From the Departments of Ophthalmology of Long Island College Hospital and Brooklyn Eye and Ear Hospital. Presented before the Brooklyn Ophthalmological Society, April 15, 1948.

† Since this article was written, at least two papers[12,13] featuring sarcoidosis of the orbit have appeared.

Clinical picture of sarcoidosis

Considering the widespread distribution of its lesions, sarcoidosis is an unusually benign condition. Those afflicted, as a rule, enjoy "good health" and are free from systemic symptoms. Occasionally a low-grade fever may persist over a period of weeks or months which suggests tuberculosis or brucellosis. Occasionally the oculist is consulted because of some eye involvement. The skin lesions may bring the patient to the dermatologist as the first consultant. At other times, the disease is first diagnosed by the roentgenologist during the viewing of X-ray studies of the hands, feet, or chest. Once a clue has been discovered in these ways, further examination of the patient will usually reveal other confirmatory findings.

Although there is a widespread distribution of the condition throughout the body, the location of the lesions is unpredictable. Thus, one patient may have sarcoidosis of the skin, lungs, and bones, whereas, another may have it of the eyes, lymph nodes, and liver. Of course there may be much overlapping of cases with regard to bodily locations of the lesions.

Sarcoidosis is essentially a disease of the reticulo-endothelial system. For this reason one is not surprised at its widespread distribution.

Skin

Of 35 cases of sarcoidosis reported by Reisner, 14 (40 percent) had skin lesions.[13] There are two types of lesions characteristically found in the skin. These are the superficial and deep. The superficial lesions are papular and nodular elevations, neatly defined, reddish, and surrounded by a zone of superficial scaling. They may vary in size from 1 to 10 mm. The deep lesions are present as subcutaneous, firm, nodular masses measuring from 5 to 20 mm. in diameter. The sites of predilection for these skin lesions are on the face, extensor surfaces of the arms and legs, shoulders, and trunk. The face lesions may involve the lids. Usually there is no subjective complaint associated with these lesions.

Lymph nodes

These may be generally enlarged over the entire body. On the other hand, there may be specific groups of such enlargements in various parts of the body. Thus, the submaxillary or inguinal may be the only groups affected. Occasionally the mediastinal nodes are alone involved and these may be detectable only by X ray. Reisner found the lymph nodes involved in all of his 35 cases. Woods and Guyton,[4] on the other hand, noted that in 15 cases of sarcoidosis three had generalized lymphadenopathy, nine had a "few" nodes, and three had no nodes enlarged.

Lungs

Characteristically, there is an infiltration of the parenchyma with the granulation tissue. This occurs mainly in the hilar regions and in the lower lobes. In 10 percent of patients with sarcoidosis of the lungs, tuberculosis develops.[4] This may be attributed to malfunction and stasis of the lungs produced by the sarcoidal involvement. Apparently this is a secondary result. The general opinion is that sarcoidosis is not a tuberculous infection, nor does it ever metamorphose into the disease. Thirty-three (94 percent) of Reisner's 35 cases had pulmonary sarcoidosis.

Bones

Occasionally there may be swelling and tenderness over the bones of the hands or feet as a result of sarcoidosis. More frequently, however, the diagnosis of bony involvement is made by X-ray films, which may have been taken to confirm the diagnosis of sarcoidosis; or the X-ray diagnosis may have been purely a fortuitous finding in examining for some other condition, such as fracture. Characteristically, the lesions are found in the small bones of the hands and the feet. The X-ray picture in these locations

resembles gout more than any other disease. Cystic and punched-out areas of decalcification may be seen in the bones of the hands and feet. Reisner found bony involvement in nine (26 percent) of 35 cases of sarcoidosis.

Liver and spleen

According to Guyton and Woods,[4] 50 percent of patients with sarcoidosis have these organs enlarged. The pathologic process consists of an infiltration of these organs with the typical granulation tissue.

Parotid glands

These are not infrequently involved in sarcoidosis. The relationship between Mikulicz syndrome and Heerfordt's disease (uveoparotid fever) and sarcoidosis has been noted by several authors.[4, 9, 13, 14] Pathologic examination of the parotid glands with sarcoidosis disclosed the typical lesion. Four (11 percent) of Reisner's cases had parotid involvement.

Heart, muscles, meninges, and other organs

Reports have been presented to show the pathologic process occurring in almost every part of the body, including the ones mentioned. In the vast majority of instances there are no clinical signs or symptoms referable to the disease in these organs. Since spontaneous remission occurs, it is possible for some of these patients to have had involvements which were not present at pathologic examination because of complete clearing of the disease.

Laboratory findings

The three most outstanding laboratory findings are the presence of false positive Wassermann reactions, an anergy (that is, lack of response) to tuberculin, and an increased globulin fraction of the blood. Other findings, such as an occasional moderate eosinophilia, an increased sedimentation rate or a hypercalcemia are less indicative of the condition. X-ray findings have been mentioned under organ involvements.

Eye findings

Levitt[9] compiled 100 cases of sarcoidosis in the literature. Forty-three of these had involvement of the eye. Of these, 28 had uveal involvement, 10 had phthisis bulbi (possibly an end result of uveitis), nine had lacrimal gland involvement, seven had involvement of the skin of the lids, and six had the disease in the conjunctiva. No mention is made of orbital involvement with sarcoidosis as a separate entity.

Means of detection of the disease

Because of the lack of subjective symptoms in this disease, patients may harbor it for long periods of time before consulting a doctor. Occasionally skin or eye disease will cause the condition to be noticed. The radiologist looking for traumatic or other pathologic condition of the extremities or during examination of a routine chest plate may note the condition. Corroboration can usually be obtained by further study of the patient.

Pathology

The essential findings of sarcoidosis, regardless of the tissue in which it is found, are always the same. It consists of a granulation tissue composed mainly of epithelioid cells with some giant cells interspersed. Eosinophiles are frequently present. A modest sprinkling of lymphocytes and fibrous-tissue proliferation may also be seen on the microscopic section. Because of the tubercle-like formation, the section resembles very closely one of tuberculosis; the two outstanding differences are the lack of caseation and the absence of tubercle bacilli.

Case report

A. E., a 44-year-old Negress, a domestic worker, born in the United States, came to the Eye Clinic of the Long Island College Hospital on August 11, 1947, complaining of a lump behind her left upper lid. This had

appeared two months previously and had been increasing progressively in size. The lesion had never been painful or inflamed. It had always been hard to the touch. The only complaints referable to the eyes were an occasional mild itch in both eyes for the past two months and some pain in the left eye on exposure to bright sunlight for the same period. Otherwise she felt perfectly well.

Past history. She had always enjoyed good health but, in 1943, a blood test routinely performed showed that she had syphilis and antisyphilitic injections were started. After receiving 17 injections in her hips and arms, the patient failed to return for further treatment. One month before admission to this clinic she was again found to have "bad" blood on routine blood testing. At this time she received four injections of penicillin, but refused to go for further treatment.

Family history. There was no evidence of syphilis, tuberculosis, or tumor formations.

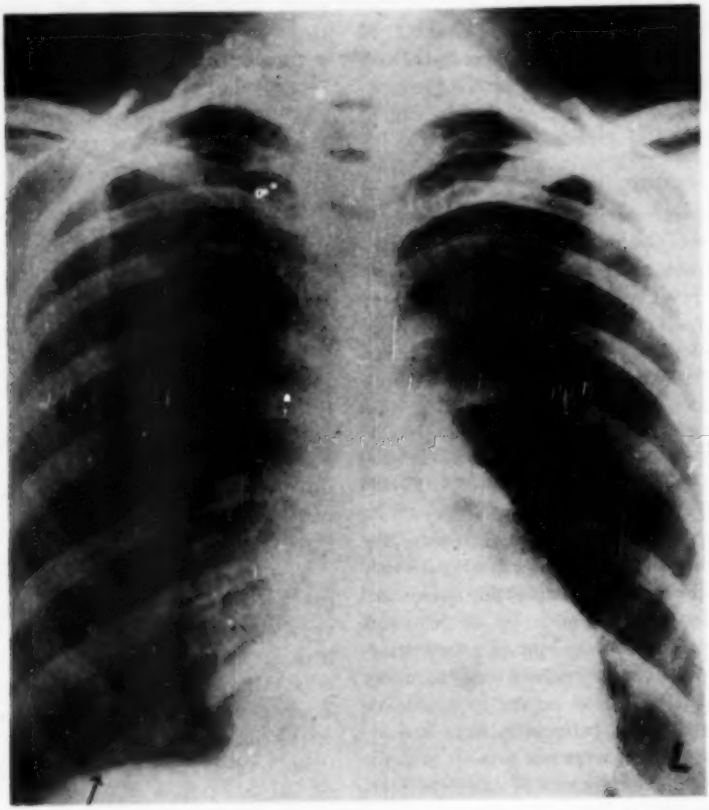

Fig. 1 (Bodian and Lasky). The lungs displayed prominence of the right hilum with some perihilar infiltration. There was a slight increase in the bronchial markings of the right lower lobe.

Physical examination. The patient was a well-developed and well-nourished Negress in no apparent discomfort. Temperature was 99°F., pulse 80, respirations 20, blood pressure 134/84 mm. Hg. Skin showed no evidence of disease. No subcutaneous lymph nodes could be palpated. Head was normal in

size and shape. Ears, nose, and throat showed no pathologic condition. Heart and lungs were normal to percussion and auscultation. Abdomen exhibited no tenderness, visceral enlargements, or masses. Extremities had no swellings, tenderness, or edema.

Eye examination. Behind the left upper lid closer toward the outer canthus was a hard mass, 30 by 15 mm. This was freely movable and not fixed to overlying skin. No tenderness could be elicited. All other structures of the eye seemed normal. No evidence of episcleritis, uveitis, or other lesions was found. Media were clear and fundi normal. Extraocular motility was normal.

Laboratory findings. Blood sugar on August 15, 1947, was 88 mg. percent. Urine and blood counts showed no pathologic findings. A Wassermann test on September 15th, was doubtful. A Mantoux test on September 22, 1947, was negative to 1/100,000 mg. of O.T. The same result was obtained with 1/10,000 mg.

X-rays. Studies on September 17th:

CHEST. The heart showed a minimal enlargement suggestive of rheumatic involvement. A very slight tortuosity and elongation of the aorta were also noted. The lungs displayed prominence of the right hilum with some perihilar infiltration. The latter findings were considered suggestive of sarcoidosis. There was a slight increase in the bronchial markings of the right lower lobe (fig. 1).

HANDS. Areas of osteoporosis with punched-out foci were present at the terminal portions of both first metacarpals. They were more pronounced on the right. These findings are typical of the bony changes seen in sarcoidosis. Evidence of old healed fracture of the left forefinger in the proximal phalanx and possibly of the left fifth metacarpal was seen (fig. 2).

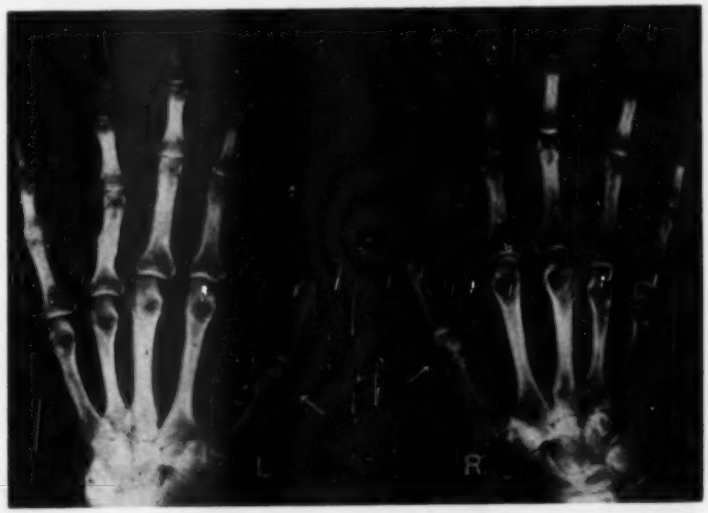

Fig. 2 (Bodian and Lasky). Showing punched-out foci of osteoporosis at terminal portions of both first metacarpals.

FEET. Bilaterally there were spherical areas of decreased density about the terminal medial portions of the first metatarsal and first proximal phalanx. This was more marked on the right. These findings were considered consistent with sarcoidosis (fig. 3).

ORBITS. No evidence of bony destruction or other pathologic process of the orbit could be discerned.

Course. The patient was admitted to the Long Island College Hospital on August 14, 1947. On August 15th, she was started on injections of 300,000 units of penicillin in beeswax and peanut oil daily for the treatment of her apparent syphilis. This was given for a period of 10 days (total of 3 million units).

On the same day, August 15th, the tumor behind the left upper lid was excised. This was done without difficulty through a horizontal skin incision in the eyebrow. Blunt dissection was adequate for most of the surgery. The deep surface of the mass was in close approximation to the conjunctiva of the upper cul-de-sac. Other than this, it was sharply defined and easily separated from all surrounding structures. The mass was sent to the pathology laboratory for study. Skin closure was made with interrupted black sutures. The postoperative course was uneventful and the patient was discharged from the hospital on August 21, 1947, one week after admission.

Pathology report (Dr. J. Arnold DeVeer). "A granulomatous mass, typical Boeck's sarcoid" (figs. 4, 5, and 6).

Follow-up in the clinic disclosed that the patient had a slight amount of diplopia on upward gaze which gradually cleared as healing progressed.

On September 22, 1947, it was noted that two small, firm, orbital masses were present behind the upper lid of the right eye. The larger was temporal. September 26, 1947, was her last visit to the Long Island College Hospital Eye Clinic, at which time there was no recurrence of tumor formation in her left eye, but the right eye was apparently unchanged.

We heard no more from this patient until October 21, 1947, when she appeared at the eye service of Dr. Walter V. Moore* of

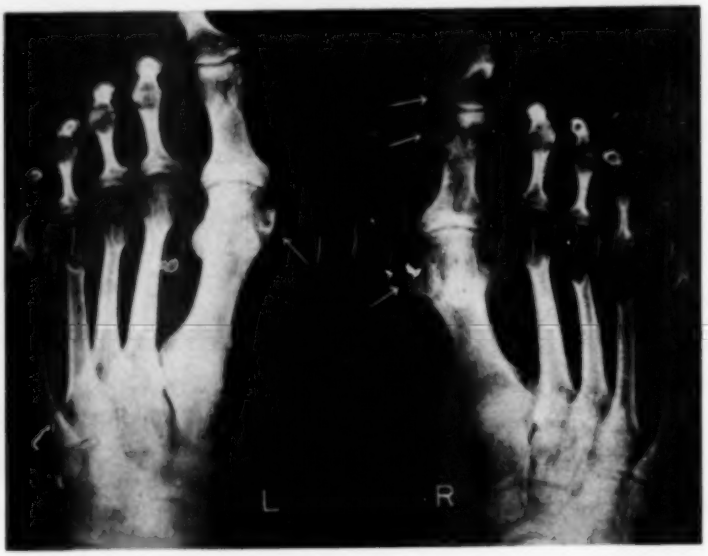

Fig. 3 (Bodian and Lasky). Bilaterally there were spherical areas of decreased density about the terminal medial portions of the first metatarsals and first left phalanges.

* We are indebted to Dr. Walter V. Moore for the use of his clinic material.

Brooklyn Eye and Ear Hospital. At this time she concealed the fact that she had been treated at the Long Island College Hospital, and gave no clue to the treatment given her. Her complaint was a mass behind the right upper lid. This had been present for three months and growing larger, especially for the last month.

Examination of her eyes showed a mass behind the right upper lid which was lobulated, firm, nontender, and freely movable. The overlying skin was not fixed. The larger portion of the mass was temporal. Smaller similar masses were felt behind the lower lids near the outer canthi. The old operative incision of the left eyebrow was well healed and not noticed. No vertical diplopia was present. There was no recurrence of any mass behind the left upper lid. Because the lesion of the right upper lid was becoming unsightly in its size and also for diagnostic purposes, it was decided to have it removed.

The patient was admitted to Brooklyn Eye and Ear Hospital on October 30, 1947, on which day she had an operation performed for the excision of the tumor mass. Local anesthesia was applied to the right upper lid by means of procaine injections. The tumor was easily shelled from its surrounding tissue by blunt and sharp dissection. It measured 1.5 cm. in diameter and was 4 cm. long. The color was pink-yellow. Because of its density and grittiness it was difficult to cut with a knife. The mass was sent to the laboratory for examination.

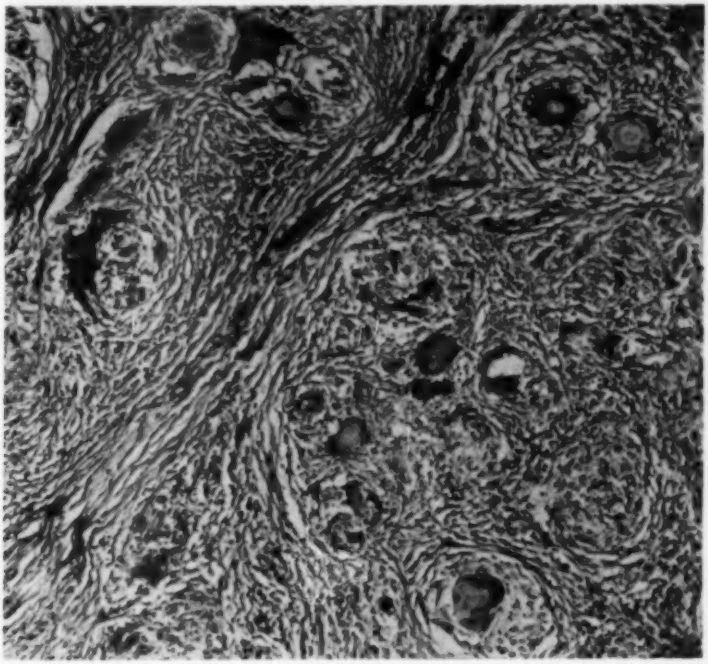

Fig. 4 (Bodian and Lasky). Section of orbital tumor removed from patient, A. E., showing typical pathologic picture of sarcoidosis. Low-power magnification shows general architecture of tumor tissue (×95). Giant cells and tubercle formations are plentiful. The absence of caseation is notable.

The pathology report (again made by Dr. J. Arnold DeVeer) was "typical of Boeck's sarcoid." The patient was discharged from

the hospital five days after admission with the wound healing well.

To complete our studies additional tests were done. These included a Kahn test of the blood, which was plus-minus in reaction. Because of this doubtful report a Laughlin test was done and found to be positive. On November 14, 1947, a Mantoux test with 1/100 mg. O.T. was "slightly positive" in 48 hours. On October 30, 1947, a conjunctival smear was negative for leukocytes or organisms. Physical examination showed a blood pressure of 160/90 mm. Hg, but all other systems, including lungs, skin, lymph nodes, and abdominal organs were perfectly normal.

The operative site healed uneventfully and when last seen (two months after her last and four months after her first operation) there was no evidence of recurrence of the masses in either upper lid. However, the lesions behind the lower lids seemed to be growing larger. Advice to the patient to return to the clinic for follow-up was not heeded.

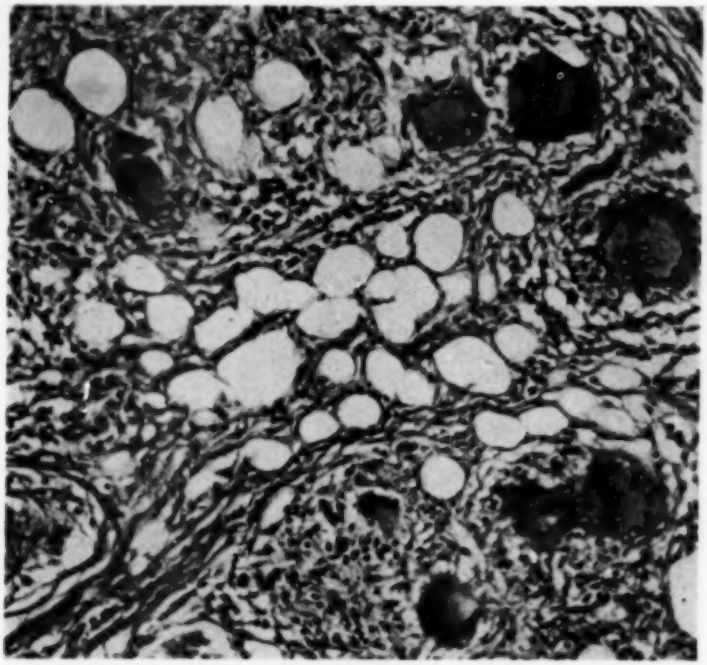

Fig. 5 (Bodian and Lasky). Higher magnification of sarcoidal tumor removed from patient, A. E. Fibrosis and round-cell infiltration may be noted about tubercles containing giant cells (×190).

Discussion

From the available literature we must conclude that the cause of sarcoidosis remains unknown. The argument of whether or not tuberculosis is the cause seems to have been won by the "nayes." However, even those who take the negative side profess to keep an open mind on the subject. Against an acid-fast etiology are the following factors:

1. Direct smears, cultures, and animal inoculations have been uniformly negative for the organism.

2. Sarcoidosis involves many widespread

and unrelated systems simultaneously; whereas, tuberculosis is rarely found in more than one organ at a time. For instance, typical bone tuberculosis is practically never associated with infection of the eyes, lungs, or peripheral lymph nodes, unless miliary spread supervenes.

7. General symptoms, such as fever, weakness, lassitude, are unusual in sarcoidosis as compared to tuberculosis.

8. The site of involvement of the lungs is

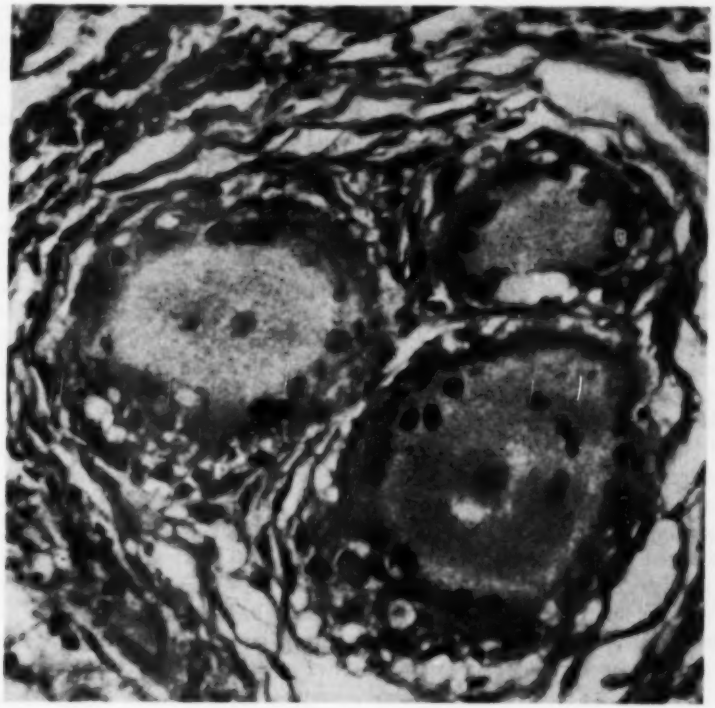

Fig. 6 (Bodian and Lasky). A single tubercle containing three giant cells separated by fine strands of fibrous tissue. A round-cell infiltration surrounds the fibrous tunic of the tubercle. Taken from orbital tumor mass removed from patient, A. E. (×420).

3. Untreated sarcoidosis tends to spontaneous disappearance. Tuberculosis of an organ tends to progress—frequently even under proper treatment.

4. Caseation is not part of the pathologic process in sarcoidosis; whereas, it is characteristic of tuberculosis.

5. Family histories have thus far been negative in sarcoidosis—unlike tuberculosis.

6. The tuberculin tests have demonstrated a relative anergy in sarcoidosis—some cases failing to react to 10 mg. of tuberculin given intracutaneously[4]—also unlike tuberculosis.

toward the bases in sarcoidosis; whereas, it involves the apices characteristically in adult tuberculosis.

Even though the exact cause for the disease has not been ascertained it seems likely that an infectious agent is responsible. Several facts point in that direction: (1) The globulin fraction of the serum is elevated; this protein element is the one which contains the antibodies of the blood and in-

creases usually in response to an infectious agent; (2) the false positive Wassermann reaction possibly suggests a response to some pathogenic organism; (3) the sedimentation rate is increased—also suggestive evidence of infection; (4) the growth of tuberclelike structures along the course of a healed corneal incision in Levitt's case "suggests the direct inoculation of the wound at the time of operation"[9] (This eye had been operated on for secondary glaucoma from sarcoidal uveitis); (5) the tendency to spontaneous healing may indicate the development of specific antibodies against a living agent.

A case is cited by German[15] wherein a skin lesion microscopically identical to sarcoidosis was produced in response to traumatically imbedded particles of silica. The localized nature of this lesion, as well as other factors, makes it unlike sarcoidosis in all other respects.

Two cases with lacrimal gland enlargement were noted by Reisner[12] in a group of 35 sarcoidosis patients. Wexler[16] reports a case with bilateral lacrimal-gland involvement which was confirmed by pathologic study. Walsh,[17] Scott,[18] Stallard,[19] and others have described swellings of the lacrimal gland associated with sarcoidosis.

In a number of instances microscopic study has shown the typical pathologic processes pervading the glandular structure. None of these observers report the presence of orbital masses separated from the lacrimal gland in sarcoidosis.

The only reference to sarcoidosis of the orbit as a separate ocular entity was made by King[20] in 1939. His patient was a 64-year-old white woman who complained of "a little lump under the lower lid of the left eye" present "for about a week."

Examination of the eye was essentially negative except for a firm nodular mass, one cm. diameter, beneath the conjunctiva and projecting up behind the globe into the lower fornix. An X-ray study of the orbit showed only increased density in the region of the growth. The mass was removed surgically and it was found to be two cm. long and one cm. in diameter. Healing was uneventful.

Dr. Verhoeff's pathologic report stated that the material was "typical of Boeck's sarcoid." Further examination of this patient showed involvement of the lungs, lymph nodes, enlarged liver, and neurologic findings affecting her left leg. A seven-year follow up showed no recurrence of the orbital condition and a spontaneous clearing of the lungs.

Commenting on this case King remarks, ". . . Judging from the literature, this is the only case in which a sarcoid tumor mass of the orbit has been found in the literature."

Since that time (1939) the literature has failed to mention a similar orbital mass. For this reason we feel that the case we have presented is of unusual interest.

In 1933 Wilmer[21] presented a 56-year-old white woman who had hard palpable masses behind the right lower and left upper lids. Episcleral lesions were also present over the insertions of the right medial and lateral rectus muscles. Biopsies of the orbital lesions showed typical tuberculous tissue in which were found "numerous spots of caseation." Apparently lesions resembling sarcoidosis were found nowhere else in the body. Discussing this case, Dr. F. H. Verhoeff stated that he had "seen several cases of Boeck's sarcoid but in none of these was the conjunctiva or orbit involved." This statement is in keeping with the rarity of orbital sarcoidosis noted in the literature.

Those who believe in the tuberculous nature of sarcoidosis might find some comfort in the findings of this case of Wilmer's but the resemblance is meager. The presence of caseation and absence of generalized bodily involvement practically exclude a diagnosis of sarcoidosis.

The patient we have presented is unusual in having multiple sarcoidal masses of the orbit, two of which were proven by pathologic study. The eyes were otherwise not involved. Generalized typical sarcoidosis was present.

Summary and Conclusions

A brief review of the published work on sarcoidosis is presented. A voluminous literature continues to bring to light new facts on the etiology, course, and clinical manifestations of the disease.

A case of typical sarcoidosis, with lung, bone, and orbital involvement is presented. The unusual feature of this case is the presence of sarcoidosis masses in the orbit. Otherwise the eyes and their adnexas were apparently free of the process. Excision and pathologic examination of two of the four orbital tumors showed the typical pattern. This included tubercle formation with epithelioid and giant cells and the absence of caseation.

King, in 1939, described the only other case of "pure" orbital sarcoidosis noted in the literature. His case had a single orbital mass. Our patient had four such bodies.

Arguments against the tuberculous nature of sarcoidosis are presented. Reasons for believing this entity has an infectious nature are also put forth. The etiology remains unknown.

349 Eastern Parkway (16).
One Nevins Street (17).

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REMOVAL OF PALPEBRAL PORTION OF LACRIMAL GLAND THROUGH THE SKIN*

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In 1929 I described my modified canthotomy.[1] This operation differs from an ordinary canthotomy principally in the fact that the external angle of the palpebral fissure is not sectioned in the horizontal plane. To the contrary, the angle itself remains whole and the taut and shortened canthal ligaments of the upper and lower lid (in cases of trachoma, and so forth) are cut off through a vertical intermarginal wound at the external canthus.

Once, when performing this operation, I probably did it a little too radically, as lacrimal gland tissue was seen on the bottom of the wound.

The idea then occurred to me that this method might be more suitable for the removal of the palpebral portion of the lacrimal gland than the one first introduced by de Wecker[2] (1888), which, as far as I know, is recommended by all textbooks: extirpation of the gland from the interior surface of the lid through an incision made in the lateral part of the cul-de-sac. The well-known and much feared disadvantage of such an incision is that some small strip of gland or tissue remains between the edges of the wound or immediately behind it, or that the conjunctival wound, when sutured, remains slightly open at some place. Thus, a permanent lacrimal fistula may arise to maintain a state of irritation and even to cause a prolonged conjunctivitis.

After having used a vertical canthotomy incision in a few instances, I noticed that this surgical approach was not particularly easy, chiefly because there was not room enough for free manipulation. On this account I transferred the incision from the intermarginal space entirely to the skin. All difficulties then disappeared.

As this method has now been used at our clinic for approximately 10 years, it seems right to report on our experience. A further reason for publication was found in the article published by Émile Haas[3] in which he reports a rather unusual method of removing the orbital lacrimal gland through the skin.

OPERATIVE PROCEDURE

Our method for removing the palpebral portion of the lacrimal gland is:

An incision, 10 to 12 mm. long, is made in the skin immediately above the superior margin of the external canthal ligament. It passes at the level of the palpebral skin fold and parallel to it. One-half of the incision is on the nasal side of the orbital margin and the other half is lateral to it. It is advisable to mark out this incision prior to the operation and the stretching of the skin. The wound is now dilated with a lacrimal-sac speculum and the muscle fibers and other tissues are dissected free rather bluntly.

Proceeding deeper and rather straight in the anteroposterior direction it is not long before the first tubuli of the palpebral gland are seen on the bottom of the cavity. The glandular tissue is there readily recognized by its oval tubulated appearance.

Gripping it with suitable forceps, the gland quite easily follows the pull. But it may also break off and, therefore, it is well to separate it from the surrounding tissue before its posterior end is finally severed with scissors. If the grip loosens or only a part of the gland is removed, there is no difficulty in finding the residual gland tissue and then removing the gland bit by bit.

Really the only important fact to remember when separating the palpebral gland from the conjunctiva is that the ducts of the orbital gland passing through the palpebral gland are firmly adherent to the surrounding tissue not only to the area of the

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upper fornix, but sometimes even to the external angle and below it.

Thus, when the gland is pulled with the forceps, the conjunctiva will also rise with it. If the medial margin of the gland is then confidently sectioned to separate it from the conjunctiva, we may at the same time cut a hole in the conjunctiva of the fornix—which is exactly what we wish to avoid. The inner wall of the gland must thus be carefully separated from its basic tissue, the ducts being severed in such a way that the conjunctiva remains intact.

As a special precaution I have used a subconjunctival bridle suture (placed between the conjunctiva of the cul-de-sac and the medial wall of the gland) covering at least the whole area of the gland. The suture is placed before the operation. For the same purpose a pair of forceps with particularly broad ends may be used.

By this bridle suture or by the forceps, the conjunctiva of the cul-de-sac can be prevented from rising conically when the gland is being pulled forward through the wound. At least it is easier by their aid to determine how far the conjunctiva of the fornix has risen in each phase. Thus the danger of penetrating the conjunctiva in extirpating the gland becomes fairly slight.

Because of the firmness of the ducts, blunt separation is not successful in the area of the gland wall, but the ducts with their surrounding tissue must be separated with scissors or a knife.

When this has been accomplished, the operation is complete except for one small suture with which the cutaneous wound is closed.

No postoperative treatment is needed except an eyepad. Since the operation is performed so laterally and through a small oblique incision, no injury to the aponeurosis of the levator or to the fascia tarso-orbitalis that might result in ptosis need be feared.

It is also possible to remove through the same incision part of the orbital gland, if the incision is elongated and the wound enlarged inward. To remove the entire orbital portion the surgical approach must be higher up, immediately below the superior temporal margin of the orbit which must still be considered the routine procedure for that purpose.

The indications for extirpation of the lacrimal gland are well known and comprise, in short, cases of otherwise incurable epiphora.

In our clinic, extirpation has mostly been performed for correction of epiphora following the removal of the lacrimal sac, and it was almost the routine procedure before Toti's[4] operation was introduced. Extirpation of the gland has not been common, however. During the last 30 years only 63 such operations have been carried out here. The method herein described has been used 26 times (22 patients).

The fact that removal of the gland has not been undertaken more frequently, although there are quite a number of cases in which the ordinary treatment is futile, can scarcely be attributed to anything else than to the results not always being satisfactory. One factor which has reduced the number of these operations in recent years is probably that dacryocystorhinostomy is now generally used here instead of extirpation of the lacrimal sac.

In his publication Émile Haas[3] has recommended the removal of the orbital portion of the lacrimal gland as a routine procedure for correction of epiphora in the cases mentioned. He even considers it important that the palpebral gland remains fully intact during the operation and claims that the epiphora will, of course, be corrected, as the gland which produces nine tenths of the lacrimal secretion is removed. Haas doesn't give the number of patients treated by this surgery.

Theoretically, it seems that extirpation of the palpebral portion of the lacrimal gland should have almost the same effect as extirpation of the orbital portion, because all the ducts of the latter are then eliminated to-

gether with the palpebral gland. The idea that the gland atrophies when its ducts are sectioned is not new. It forms at least partly, the basis of the operation recommended by Jameson,[5] which we have termed canaliculotomy: Through an incision in the conjunctival surface of the lid all ductules of the lacrimal gland are sectioned subconjunctivally in the area of the fornix.

In 10 cases I combined this canaliculotomy with extirpation of the palpebral gland and, in a few cases, it was the sole surgical procedure; each time the operation was performed through the skin. It seems to be less effective for correcting epiphora than one would expect. For that reason I am inclined to doubt whether the gland actually becomes atrophied as a result of the cutting off of the ducts, although for instance Stock[6] makes the short, definite statement "die orbitale Tränendrüse atrophiert infolgedessen."

It seems to me that the first thing a gland does after such surgical interference is to begin to produce new, as it were, substitute ducts. In some as yet unknown way these ducts also seem to be able to bring tears into the eye. It is also possible that the accessory (Krause's) lacrimal glands may increase their activity and perhaps change in size (or even increase in number) in such cases.

On the basis of what has been said, it is understandable that extirpation of the palpebral lacrimal gland has not been done more often here, although we now have, in my opinion, an operation for that purpose which is easy to perform.

Based on the experience obtained it may be stated briefly that extirpation of the palpebral portion of the lacrimal gland performed according to this method gives a fairly satisfactory result in about 65 to 70 percent of cases of epiphora. In the others, epiphora continues for reasons all of which are not known at present.

In evaluating the results of the operation, the patient's subjective opinion is almost a more reliable criterion than Schirmer's[7] test. I have come to the conclusion that the irritation caused by the litmus of congo paper used for measuring the degree of wetness varies in the individual cases depending on the sensitiveness of the eye. Thus the wetting of the paper measured in millimeters does not always give the right conception of the wetness of the eye and the discomfort it causes the patient.

The danger of the eye becoming too dry following a removal of the palpebral gland does not seem probable. If that happens, it seems that the patient must have some other disease predisposing to a dry eye.

Summary

A method is suggested for the removal of the palpebral portion of the lacrimal gland. This method leaves the conjunctiva of the fornix intact and exposes the gland from the cutaneous side.

It must be remembered that the conjunctiva of the cul-de-sac adheres to the gland and that, when the gland is dissected out, there is danger of puncturing the conjunctiva unless it is grasped with broad-pointed scissors or a subconjunctival bridle suture is placed.

Good results have been obtained in 65 to 70 percent of the cases of epiphora in which this operation is indicated.

Schirmer's test is not a reliable test for epiphora.

Lapinlahdenk 3.

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THE AUTOCLAVING OF DRUGS FOR USE AT THE TIME OF INTRAOCULAR SURGERY*

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The proper method for the sterilization of drugs to be instilled in the eye immediately before, during, or after intraocular surgery is controversial. The methods of drug sterilization differ from hospital to hospital throughout the country. Certain practices may be based on scientific study; whereas, most drug sterilization, if it is done at all, is left to the discretion of the nurse in charge, or is the result of advice given by the surgeon on conflicting or hearsay evidence. In many hospitals drugs, which have been prepared by the pharmacist under as clean conditions as possible, are instilled in the eye at the time of surgery. This obviously is not a proper procedure.

Sterilization is commonly carried out by mechanical filtration, by means of chemicals, or through the use of heat.

Sterilization by mechanical filtration

According to Parke, Davis & Company,[15] the overheating (above 120°C.) of epinephrine chloride for more than 20 minutes results in a breakdown of the epinephrine making it ineffective, hence the bacterial filtration method of sterilization is employed. The solution is passed through sterile filtering candles of the Berkefeld type. These special filters, the maximum pore having a radius of 0.85 micron, remove even the most minute bacteria and have an additional advantage in that they can be easily sterilized by heating until red hot.

Immediately after filtration, the solution is tested for sterility as a check on the process. This method, specifically indicated for solutions which will not stand heat or chemical sterilization, is obviously too detailed and technical for the average hospital to carry out.

Sterilization by chemicals

Numerous preservatives and antiseptics are used in ophthalmic solutions. Boric acid retards the growth of microörganisms but rarely destroys pathogenic bacteria. Hasler[10] recommends the use of the ester derivatives of benzoic acid. These esters in combination, 65 parts Nipagin-m and 35 parts Nipasol-m, are nontoxic and nonirritating to the eye, kill Staphylococcus aureus in 24 hours, and prevent growth of fungi. Chlorobutanol, camphor, and menthol are also frequently employed as preservatives.

McPherson and Wood[13] have shown that benzalkonium chloride (zephiran) in a concentration of 1:5,000 maintains the sterility of ophthalmic solutions for at least two weeks. Staphylococcus aureus, Escherichia coli, and Bacillus pyocyaneus were introduced into this 1:5,000 solution, and none of the organisms survived after two minutes.

Benzalkonium chloride is stable and long acting even after high dilution with tears and is unaffected by freezing or boiling. It is compatible with most drugs, but there are exceptions, among those being silver nitrate, sulfathiazole sodium, pilocarpine nitrate, and physostigmine salicylate.

The widely used buffers of Gifford and Smith[8] are incompatible with benzalkonium chloride but the monobasic potassium phosphate and dibasic sodium phosphate buffer of Arrigoni and Tozer[1] is compatible, as is the sodium acid phosphate and disodium phosphate buffer of Hind and Goyan.[11]

Recently Hughson[12] reported on the use of alkyl dimethyl benzyl ammonium chloride (zephiran) for maintaining the sterility of solutions. He concluded that zephiran

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chloride in a concentration of 1:5,000, used as a vehicle for atropine sulfate, physostigmine sulfate (the salicylate is incompatible), pilocarpine hydrochloride, and tetracaine hydrochloride, preserves the sterility of these drugs for as long as 19 days.

The toxicity of this chemical agent was ascertained by replacing the aqueous of rabbits' eyes with zephiran chloride 1:3,000, 1:6,000, 1:7,500. The 1:3,000 and the 1:6,000 concentrations produced an endothelial edema which disappeared in from 6 to 8 weeks. The 1:7,500 concentration produced no slitlamp evidence of damage.

Swan,[20] however, found that the injection of zephiran, in a concentration of 0.025 percent (1:4,000) to 0.050 percent (1:2,000), into the anterior chambers of eyes of albino rabbits resulted in a violent reaction. Biomicroscopy revealed a swollen, gray corneal endothelium, and, in some instances, vesicles were observed to form and rupture leaving Descemet's membrane exposed.

Engorgement of the iris vessels and edema of the iris stroma occurred, but lens opacities did not develop. The acute inflammatory process subsided in a few days, and, in several instances, degeneration and secondary glaucoma occurred. The cornea seldom returned to normal, and, in many instances, became opaque and vascularized. Swan concluded that a wetting agent such as zephiran injected into the anterior chamber even in minute concentrations produced violent reactions.

Comment

Inasmuch as benzalkonium chloride might be accidentally introduced into the anterior chamber of the eye at the time of surgery, and because there exist differences of opinion and of experimental evidence as to its toxicity, it is believed that the sterilization of drugs to be used at the time of intraocular surgery should be brought about, when possible, by means other than chemicals.

Sterilization by Heat

Sterilization by means of heat may be carried out by tyndallization, boiling, or autoclaving.

Tyndallization

Davis[7] states that atropine sulfate and physostigmine salicylate, due to their instability, should be tyndallized, that is, heated to 80°C. for one hour for three successive days. Coulthard[6] believes that heating epinephrine chloride to 80°C. for one hour is sufficient to sterilize the solution.

Boiling

Questionnaires were sent to the members of the Section on Ophthalmology of the American Medical Association and, as tabulated in the results, 75 percent of those circularized reported[4] that they felt that boiling did not affect the anesthetic properties of cocaine. Several clinicians were asked to compare the effects of boiled and unboiled solutions of cocaine and reported no difference in their anesthetic power. They believed, however, that repeated boiling or steam sterilization caused a diminution of cocaine content which decreased the activity of the solution.

Regnier, Liot, and David[17] found that a solution of cocaine hydrochloride, sterilized at 100°C. and preserved during a period of several months, lost only a small part of its anesthetic value and gave results comparable to a freshly heated solution.

Nordlöw,[14] in carefully controlled experiments, using a two-percent aqueous solution of cocaine hydrochloride heated 5 to 10 times for 20 minutes by boiling, and testing the anesthetic effect on human corneas with von Frey hairs, found no lessening of the anesthetic effect.

Regnier and David,[16] however, reported that cocaine hydrochloride heated one hour at 100°C. lost 100 percent of its anesthetic power.

The evidence regarding the ability of cocaine to withstand boiling is therefore con-

flicting and inconclusive. It does seem, however, that cocaine can be boiled for a short time without affecting its anesthetic power.

Autoclaving

Skolaut[18] states that the autoclaving of drugs in rubber-capped vials is slow and tedious and the temperature of autoclaving causes marked deterioration if alkaloid salts are present.

Davis[7] found that pilocarpine nitrate can stand 10 pounds of pressure for 30 minutes without change. Of the anesthetics, Braun[3] cites Reclus as stating that Herissey found that cocaine in aqueous solution could withstand a temperature of 115°C. to 120°C. without change. It was not mentioned, however, how often or for how long cocaine could withstand this means of sterilization.

Regnier and David[16] strongly buffered a one-percent cocaine solution of a pH close to 8.2, autoclaved it at 115 to 120 pounds for 15 minutes, and then tried the anesthetic effect of the cocaine on the corneas of rabbits. The results showed that a strongly buffered solution of cocaine lost almost its entire anesthetic effect, through autoclaving.

Wilmer and Paton[22] found that pontocaine (tetracaine hydrochloride) could be autoclaved for 15 minutes at 15 pounds without altering its anesthetic effect.

Nothwithstanding the assumption that alkaloids such as atropine and cocaine do not tolerate autoclaving, Clevenger[5] states that, at the New York Eye and Ear Infirmary, eye solutions are carefully filtered into stock bottles and are covered with a circle of muslin glacine paper and a heavy paper cup and then sterilized by autoclaving for 10 minutes under 10 pounds of pressure. She failed to state which drugs could be autoclaved and which could not, or how often autoclavable drugs could be resterilized without lessening their action.

Stallard[19] autoclaves tetracaine, atropine, and cocaine at a temperature of 110°C. with a pressure of 7½ pounds per square inch for 30 minutes. He does not say how often these drugs may be autoclaved without losing their effectiveness. Stallard does, however, remark that physostigmine is unstable and cannot be autoclaved due to oxidation and must be prepared aseptically by placing the solutions in bottles which have been recently autoclaved.

Our interest was drawn to a paper by Haffly and Jensen[9] who outlined a method of maintaining the sterility of ophthalmic solutions by means of autoclaving ophthalmic drugs in rubber-stoppered serum bottles. They did not report what effect the heat had on the drugs. A series of experiments were, therefore, undertaken to ascertain which drugs commonly employed at the time of intraocular surgery could be autoclaved without greatly disturbing their properties, and how often the process of autoclaving could be carried out without appreciably altering the effect of the drug.

The preparation of an ophthalmic solution

In preparing a solution for use in the eye, physiologic activity, irritability, stability, penetrating power, buffers, isotonicity, compatibility, and the ability to withstand sterilization and remain sterile are factors that must be considered.

Physiologic activity

The physiologic activity of a solution is dependent upon the concentration of free base present. The relative concentration of free base is increased by rendering a solution more alkaline and decreased by creating a more acid medium. Most alkaloids have an optimum activity at a pH of from 7.0 to 8.0 with 7.6 being the average for most.

Irritability

A high concentration of free base is usually intensely irritating to the eye. The irritation induced may be ameliorated by decreasing, at the sacrifice of some physiologic activity, the amount of free base present. This is done by lowering the pH

of the solution. The range of comfort of an eye preparation resides within a pH range of 6.5 to 7.8, the tears having a pH of 7.4. Another means of reducing irritation is by controlling the osmotic pressure. The eye can tolerate, without apparent discomfort, a wide range of osmotic pressure when the pH is controlled. Conversely, the same is true with a wide range of pH, provided the osmotic pressure is regulated.

Stability

Aqueous solutions of the acid salts of physiologically active bases are most stable when at a pH of 2.0 to 3.0. Alkaloidal salts, at an optimum activity of pH 7.0 or above, lose from one half to all of their activity in about one month. Atropine (0.5 percent) at a pH of 8.3 loses 44 percent in 30 days.[11] It follows that a compromise between chemical stability and physiologic activity must be effected. If a solution is to be kept for several weeks, it is necessary to sacrifice maximum activity to obtain stability. On the other hand, if the solution is to be used immediately or stored in sealed chemical inactive containers, attention to stability becomes secondary.

Penetrating power

The absorption of a drug may be enhanced by increasing the permeability of the cornea. This is a complex process influenced by the molecular structure and physical properties of the drug as well as the physical properties of the vehicle. Of special importance is the degree of affinity the drug has for the vehicle. Wetting agents act by decreasing the surface tension of the cornea, thus inducing more rapid penetration of the drug. Tears are a natural wetting agent. The surface tension of water is 72.75 dynes per centimeter while that of a 1:1,000 solution of benzalkonium is 39.09 dynes per centimeter.

This drug, therefore, has an excellent wetting property and is often used for that purpose as also are the aerosols and the duponals. All, however, have toxic properties and must be used with a certain degree of caution. The absorption of a drug is also influenced by the pH of the excipient; for example, the absorption of atropine (1 percent) is increased by three times when the pH is increased from 4.4 to 7.5. Gifford and Smith[8] found by clinical tests that, although Fisher had reported that pilocarpine is best absorbed at a pH of 4.0 to 5.0, the effect on the iris of pilocarpine is greater in an alkaline than in an acid medium.

Buffers

The pH of a solution is determined and maintained by buffering. Hind and Goyan[11] modified Sorensen's phosphate buffer system by proportioning sodium acid phosphate and disodium phosphate so as to obtain a buffer range of 5.8 to 8.0 pH with a maximum buffer capacity at pH 6.7. This stable buffer system is so adjusted as to be isotonic to physiologic saline and contains no ions foreign to the eye. It is, however, chemically incompatible with zinc salts.

The buffers of Gifford and Smith[8] may be employed to give a rather wide range of pH depending upon the mixture of solutions. There is a marked tendency, in the buffer mixtures with a pH below 8.0, for the solution to become more alkaline upon standing due to the solution giving off more carbon dioxide than it absorbs.[11]

Isotonicity

In the development of an efficient ophthalmic solution, the osmotic pressure must be recognized as an important factor. To achieve isotonicity, the tears and solution must have the same osmotic pressure and identical freezing points. Hind and Goyan[11] have found that, in a series of contact lens solutions with optimum wearing qualities, the freezing point of 0.54°C. is approximately that of physiologic saline. They further state that there is little valid evidence to support the belief that a 1.4-percent solution of sodium chloride is isotonic with lacrimal fluid. They cite Krough and others

as having recently published the value of 0.90-percent sodium chloride as the osmotic concentration of lacrimal fluid. The eye may well tolerate 0.5 to 2-percent concentration and, therefore, for all practical purposes the osmotic factor must be maintained only within reasonable physiologic limits.

The four buffer solutions of Gifford and Smith[8] happen to approach fairly near to isotonicity as does that of Hind and Goyan.[11] Exact isotonicity, if desired, can be created by referring to Nicola's tables.[21] These indicate the proper amount of sodium chloride to add to create isotonicity.

The ideal solution

The ideal ophthalmic solution should be: (1) Free and remain free of microörganisms for a reasonable length of time, (2) nonirritating, (3) of optimum physiologic activity, (4) stable, (5) of low toxicity, (6) of low surface tension or of high wetting power, (7) sterilizable, (8) compatible, and (9) of low cost.

Procedure

In preparing the various solutions, an attempt was made to include as many factors of an ideal ophthalmic solution as possible. Desiring buffered, highly active, and mildly antiseptic solutions, they were prepared according to the formula of Gifford and Smith.[8] An acid buffer solution was made of anhydrous boric acid (12.4 gm.) and anhydrous potassium chloride (7.4 gm.) in 1,000 cc. of distilled water. The drug to be tested was then dissolved in the acid buffer solution. An alkaline buffer solution was then prepared by dissolving 21.2 gm. of anhydrous sodium carbonate in 1,000 cc. of distilled water. This latter solution was added to the acid buffer solution containing the drug until the desired pH was attained. The pH of each was accurately determined by means of a Beckman pH meter. One ounce of the prepared eye drops was then filtered into a 30 cc. Kimble No. 15,105 Neutraglass Serum Bottle,* the most resistant glass bottle available. This glass induces a change of less than 0.5 pH units in distilled water after being autoclaved at 121°C. for 30 minutes.

After the initial control tests were made using the freshly prepared and buffered solutions, the bottles were stoppered with rubber serum bottle stoppers and autoclaved for 15 minutes at 15 pounds pressure per square inch. A hypodermic needle was inserted into the stopper during the autoclaving to prevent a change in pressure within the bottle during the process. The pressure and temperature of the autoclave were slowly brought down over a period of 10 to 15 minutes following the autoclaving to prevent ebullition with consequent concentration of the solution. Each subsequent autoclaving was carried out in a similar manner.

Before each experimental procedure, the top of the serum-bottle stopper was swabbed with 1:1,000 zephiran chloride solution. The desired amount of solution was withdrawn through a needle into a 0.25 cc. tuberculin syringe. The needle was then removed from the syringe and, with the patient in the recumbent position and the eyelids separated, the drops were placed on the cornea.

In order to test the physiologic activity of the anesthetic solution, a von Frey's hair was constructed somewhat after the method of Bellows.[2] To do this a straight length of 4-0 horsehair was cemented to the end of a six-inch glass rod at an angle of 110 degrees. To determine the strength of the hair the glass rod was placed in a ring-stand clamp so that the hair was perpendicular to and just touching the pan of a balance. The hair was then adjusted in length so that when a 200-mg. weight was placed on the opposite pan a barely perceptible bowing of the hair was noted. With this hair a constant stimulus could be produced.

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* Glasco Products Co., 111 North Canal Street, Chicago 6, Illinois.

Anesthetics

Tetracaine hydrochloride

The patients used in testing tetracaine hydrochloride were 11 female nurses varying in age from 19 to 26 years and one male medical student, aged 22 years. With the patient in the recumbent position, the cornea was touched with the hair in five places (centrally and in the superior and inferior nasal and temporal quadrants) to test the corneal sensitivity. No attempt was made to test either bulbar or palpebral conjunctival sensitivity.

Two minims of a 0.5-percent tetracaine hydrochloride solution buffered to a pH of 5.1 were then placed on the cornea. A pH of 5.1 was chosen as that is the pH of the commercial product, pontocaine hydrochloride, of Winthrop-Stearn Company. There was no reference found in the literature indicating the pH at which tetracaine is best absorbed through the cornea.

The cornea was subsequently tested at the five indicated points after 30 seconds, one minute, and at periods of one minute thereafter. The von Frey's hair was brought down perpendicular to the cornea until the slightest perceptible bowing was noticed. The testing was continued until a stimulus was felt in one of the five tested areas.

Cocaine hydrochloride

Twelve female nurses were used to test the four-percent solution of cocaine hydrochloride which was buffered to a pH of 6.0 according to Gifford and Smith. The same procedure was used in testing cocaine hydrochloride as in testing tetracaine hydrochloride.

Miotics

Pilocarpine hydrochloride

To test pilocarpine hydrochloride, 11 female nurses were used, aged 19 to 26 years. All tests were carried out in the same medium-lighted room having two windows. No direct sunlight entered the room. The pupillary diameters of both eyes were measured and then, with the patient reclining, one minim of one-percent pilocarpine hydrochloride adjusted to a pH of 7.6 after Gifford and Smith was placed in one eye. Fisher found that pilocarpine was better absorbed at a pH of 4.0 to 5.0 but Gifford and Smith[8] presented evidence to the contrary. The pupillary measurements of each eye were again taken after 15 minutes and 30 minutes.

Early in the testings, measurements of accommodation by an accommodation rule were attempted, but due to the wide variation in the results they were considered too unreliable to use.

Physostigmine salicylate

The physostigmine tests were carried out under the same circumstances and on the same subjects as was pilocarpine. One minim of physostigmine buffered to a pH of 7.6 according to Gifford and Smith was placed on the cornea and measurements made at the same time intervals as for pilocarpine.

Epinephrine chloride

Tests using epinephrine chloride were planned but due to its marked instability as indicated by the manufacturer, experiments were not carried out.

Cycloplegic

Atropine sulfate

Atropine sulfate was prepared as outlined above in a one-percent solution and buffered to a pH to 7.6. Six rabbits were used for testing purposes, three males and three females.

In addition, tests were carried out on human subjects; six female nurses were selected, aged 19 to 27 years.

Experimental results

Tetracaine hydrochloride

Using two minims of a freshly buffered solution of 0.5-percent tetracaine hydrochloride, adjusted to a pH of 5.1, it was

found that 10 of the 12 nurses tested developed corneal anesthesia to the von Frey's hair within 30 seconds and all of them within one minute. The average duration of anesthesia for the fresh solution was eight minutes (range 14 minutes to five minutes). One patient apparently blinked the solution out of her eye as anesthesia was never attained.

After one autoclaving at 15 pounds for 15 minutes the pH dropped to 4.7. All but one achieved anesthesia within 30 seconds and the average duration of anesthesia was eight minutes and 36 seconds (range 13 minutes to four minutes).

Following three autoclavings the pH remained at 4.7 with anesthesia again achieved in all but one case in 30 seconds. The average duration of anesthesia however dropped to seven minutes 45 seconds (range 14 minutes to four minutes).

The solution was then autoclaved three more times after which the pH was determined at 4.6. Here again all but one nurse exhibited corneal anesthesia within 30 seconds. The average length of anesthesia was seven minutes and 15 seconds (range 16 minutes to two minutes).

After three more autoclavings, making a total of nine, the pH was read at 4.7. The solution had by now taken on a yellowish tinge and a slight flocculation was also seen. In spite of this, all corneas were anesthetized within 30 seconds and the average duration of anesthesia was six minutes, 20 seconds (range 11 minutes to four minutes). There was no constancy of anesthesia at any of the five corneal points tested. From these findings it was concluded that tetracaine was only very minimally affected by at least six autoclavings.

After the third autoclaving, the experiment was carried out with 11 subjects instead of 12 due to the fact that one was no longer available.

Cocaine hydrochloride

Using two minims of a freshly buffered solution of four-percent cocaine hydrochloride adjusted to a pH of 6.0, it was found that anesthesia to the stimulus of the von Frey's hair was, in most cases, attained within 30 seconds and in all cases was attained within one minute. The average duration of anesthesia for the 12 subjects tested with the fresh solution was five minutes, 25 seconds (range nine minutes to four minutes).

After autoclaving the solution 15 minutes at 15 pounds pressure, the pH dropped from 6.0 to 3.3. Using the same technique as before, it was found that eight of the 12 subjects acquired complete anesthesia after 30 seconds and all attained it after one minute, while the average duration of anesthesia was three minutes, 54 seconds (range eight minutes to three minutes).

The solution was autoclaved a second time and the pH was found to be 3.05. After a third autoclaving the pH dropped to 2.8 and the solution took on a slight yellowish tinge.

Using the thrice-autoclaved solution it was found that nine of the 12 subjects still had an anesthesia produced in 30 seconds, and 11 of the 12 within one minute. The average duration of anesthesia was three minutes, 20 seconds (range five minutes to one minute).

It was noted that with each succeeding autoclaving the solution, in addition to some slight loss of anesthetic power, caused an increased amount of irritation and stinging. For this reason it was thought that further autoclaving would only increase the irritation so the cocaine hydrochloride tests were discontinued.

There was no constancy in the loss or return of sensitivity at any of the five corneal points tested with the von Frey's hair. (It should be noted that there was a general widening of the palpebral fissure with some mydriasis throughout the experiment with cocaine.)

A repeated course of autoclaving with a fresh cocaine solution produced similar pH changes, 3.3 after one autoclaving, 3.0 after two, and 2.8 after three.

Pilocarpine hydrochloride

Before each testing of one-percent solution of pilocarpine hydrochloride bilateral pupillary measurements were taken. With the freshly buffered solution having a pH of 7.6, it was found that a marked response was evident within 15 to 30 minutes; 15 minutes after administering one minim of the drug the pupils had constricted on an average of 2.95 mm. (range 5 mm. to 1 mm.). After 30 minutes the average amount of constriction was 3.45 mm. (range 5 mm. to 1.5 mm.). All subjects experienced a blurring of vision in the eye subjected to pilocarpine. The pilocarpine solution was then autoclaved for 15 minutes at 15 pounds of pressure, the pH was recorded at 7.55, and the procedure repeated.

With this once-autoclaved solution, there was an average of 1.63 mm. constriction after 15 minutes (range 3 mm. to 0 mm.) and an average of 2.86 mm. constriction after 30 minutes (range 4.5 mm. to 1.5 mm.). Only slight blurring was evident after one autoclaving.

Following two more autoclavings, making a total of three, the pH was found to be 7.6. This, when administered, produced an average constriction of 0.86 mm. after 15 minutes (range 2 mm. to 0 mm.) and an average constriction of 1.81 mm. after 30 minutes (range 2.5 mm. and 1 mm.).

After five autoclavings the pH was found to be 7.5. The potency of the drug was by now quite reduced so that an average constriction of only 0.68 mm. was found after 15 minutes (range 2 mm. to 0 mm.) and an average constriction of only 1.45 mm. after 30 minutes (range 3 mm. to 0 mm.). No blurring was found after the third autoclaving.

In the initial tests with pilocarpine an attempt was made to determine the near point of accommodation for each subject both before and after administering the drug. The results, however, proved too unreliable to tabulate. An attempt was also made to follow the pupillary measurements for periods of 2, 4, and 6 hours, but due to the nurses' professional duties, classes, and other interruptions, a complete record was not possible.

We felt, however, that the action of the drug within the first 30 minutes was a good indication of its physiologic action and have drawn our conclusion from those findings.

Physostigmine salicylate

The freshly prepared 0.2-percent physostigmine-salicylate solution, buffered to a pH of 7.6, took on a definite pink color shortly after it was made. After taking the pupillary measurements as for pilocarpine, one minim of the solution was placed on the cornea. Fifteen minutes following its administration there was an average constriction of 2.72 mm. (range 4.5 mm. to 0.9 mm.). This was increased to an average constriction of 3.63 mm. after 30 minutes (range 4.5 mm. to 2 mm.). All subjects complained of a great deal of blurring and four suffered supraorbital and temporal pain. As with pilocarpine, attempts were made for follow-up measurements but due to the variety of duties of the subjects a complete compilation was impossible. It was found, however, that when nine of them were measured 24 hours after the drug was instilled, there remained an average constriction of 1.88 mm. (range 4 mm. to 1 mm.).

The physostigmine was then autoclaved for 15 minutes at five pounds pressure per square inch. The solution turned cherry red and had a pH of 7.66. After administering this solution, it was quite evident that it could not withstand autoclaving and retain its physiologic activity. Fifteen minutes after its administration there was an average pupillary constriction of only 0.35 mm. (range 1 mm. to 0 mm.). At the end of 30 minutes the average constriction was only 0.80 mm. (range 2 mm. to 0 mm.).

One of the subjects had inadvertently

had a homatropine refraction 4 or 5 hours preceding the test and no action at all was produced by the physostigmine.

Because of this marked diminution of activity after one autoclaving further experiments were discontinued.

Atropine sulfate

To test the stability of atropine sulfate a one-percent solution was made up as indicated previously and buffered to a pH of 7.6. Six rabbits were used for testing purposes, three males and three females. Each pupil was measured after which the lower lid was drawn out and 0.3 cc. of the solution was placed in each cul-de-sac. This was contained in each cul-de-sac for approximately 10 seconds. Pupillary measurements were made after 30 minutes, one hour, and two hours. The average increase in pupillary diameter is given in Table 1.

TABLE 1

Average increase in pupillary diameter following instillation of atropine sulfate solutions in the eyes of six rabbits

	Pupil Diameter		
Atropine Sulphate Solution	30 min.	1 hr.	2 hrs.
Fresh	2.12 mm.	1.79 mm.	1.70 mm.
Autoclaved 1 time	1.33 mm.	1.27 mm.	1.25 mm.
Autoclaved 3 times	1.04 mm.	1.54 mm.	1.36 mm.
Autoclaved 5 times	1.50 mm.	1.68 mm.	1.31 mm.
Autoclaved 8 times	1.22 mm.	1.27 mm.	1.22 mm.

The figures shown in Table 1 would seem to indicate that atropine sulfate withstood autoclaving up to eight times with relatively little loss of physiologic action. However, to substantiate these findings, tests on human subjects were carried out.

Six female nurses were selected whose ages varied from 19 to 27 years. Preliminary pupillary measurements were determined, as well as the near point of accommodation. Following this one minim of fresh one-percent atropine-sulfate solution was put in one eye of each of three nurses while a solution that had been autoclaved six times was put in one eye of each of the remaining three nurses.

Pupillary measurements and accommodative ability were determined after 30 minutes, one hour, two hours, six hours, 24 hours, and 48 hours. After 30 minutes the subjects having the fresh solution had an average pupillary dilatation of 5.16 mm., while those having the autoclaved solution had an average dilatation of 4.33 mm. Only one of the three who received instillations of the fresh solution was able to accommodate sufficiently to read the test letters on the accommodative rule and her corrected accommodative near point decreased from 11.2 cm. to 14.2 cm. The three nurses who received the autoclaved solution had an average decrease in their near point of 11.2 cm. after 30 minutes.

At the end of an hour, the fresh solution still produced an average pupillary size increase of 5.16 mm. while those having the autoclaved solution showed a slight increase in their average to 4.66 mm. None of the six could accommodate sufficiently to be tested on the accommodation rule.

Two hours and six hours following the instillations, the measurements remained the same. Twenty-four hours after instillation, all measurements were the same except in one subject who had had the autoclaved drug. She showed a decrease in dilatation of 0.5 mm. All were unable to accommodate sufficiently to read the test letters on the accommodation rule.

Forty-eight hours after instilling the drug, the pupils of two nurses who received the fresh solution showed a decrease in diameter of 0.5 mm. each. These subjects were still

unable to accommodate sufficiently to read the test letters on the accommodation rule. The three nurses who received instillations of the autoclaved atropine showed decreases in their pupillary diameters of 1.0 mm., 0.5 mm., and 1.0 mm. and one was able to accommodate at a distance of 21 cm.

Summary

Tetracaine hydrochloride in buffered solution withstood repeated autoclaving both as to duration of anesthetic power and pH. The solution continued to produce effective results after six autoclavings, losing only about 10 percent of its effectiveness based upon duration of anesthetic properties.

One autoclaving of buffered cocaine hydrochloride causes a decrease of about 30 percent of its effectiveness based upon its shortened duration as an anesthetic, as well as a marked decrease in its pH, and an increased subjective irritation. It was, therefore, believed that, while cocaine hydrochloride might still be used effectively after one autoclaving, more than that produced too acid a solution for its effective clinical use.

Pilocarpine hydrochloride lost approximately 25 percent of its effectiveness after one autoclaving and almost 50 percent of its effectiveness after two autoclavings based on its property of pupillary constriction. It is believed that one autoclaving does not contraindicate its use in intraocular surgery.

Physostigmine salicylate due to its oxidation when heated does not stand autoclaving. This was substantiated by a very marked loss in its physiologic action.

Atropine sulfate unlike other alkaloids appears to withstand autoclaving well. After six autoclavings it gave comparable results with fresh solutions when administered to rabbit and human eyes.

Conclusion

1. Most drugs employed at the time of intraocular surgery can be autoclaved at least once for 15 minutes at 15 pounds. Exceptions are epinephrine chloride and physostigmine salicylate.

2. Tetracaine hydrochloride withstood nine autoclavings with relatively small loss of physiologic action or change in pH.

3. Cocaine hydrochloride withstood one autoclaving with but only a partial loss of physiologic action and with a rather marked reduction in pH.

4. Pilocarpine hydrochloride showed a constant progressive loss of physiologic activity with successive autoclavings but showed only minimal pH change.

5. Physostigmine salicylate does not withstand autoclaving.

6. Atropine sulfate retains its physiologic activity and pH after six autoclavings.

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THE EFFECT OF THE LOCAL USE OF HOMATROPINE HYDROBROMIDE ON THE NORMAL ANGIOSCOTOMA*

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INTRODUCTION

Homatropine hydrobromide is one of the drugs most commonly employed in ophthalmology. Comparatively few studies have appeared on its actions other than cycloplegia and mydriasis. The following studies were found helpful.[1-4] It was decided to study the possible effects of this drug in relation to changes in the angioscotoma, because that defect has shown responses to a large group of therapeutic agents.[5-8]

GENERAL PHARMACOLOGY OF HOMATROPINE

Homatropine was first employed as a cycloplegic in 1881.[9] It is a synthetic alkaloid of mandelic acid and a tropine base.[1] Homatropine prevents the response of smooth muscle and gland cells to cholinergic impulses. The site of action is considered to be mainly peripheral and it prevents access of the cholinelike activating substance to the muscle cells.[10,11] The circular muscle bundle of the iris and the circular bundle of the ciliary group of muscles are innervated by parasympathetic nerve fibers conveyed by way of the third nerve. Stimulation of the nerves to these structures, therefore, causes miosis and accommodation for near objects respectively. Homatropine, by inducing paralysis of the parasympathetic nerves to these structures, causes mydriasis and accommodation for remote objects.

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Methods and Materials

Angioscotometry is the study of visual field defects "radiating from the blindspot of Mariotte and related in form to the pattern of distribution of the retinal vessel tree."[13] These field defects are modified by changes in the retinal perivascular spaces and synaptic junctions.

The subjects of the study were members of the professional staff of the Long Island College Hospital ranging in age from 23 to 32 years. There was no evidence of local or systemic disease; no evidence or history of previous ocular disease could be discovered on slitlamp or ophthalmoscopic examination or by questioning. Refractive errors were of moderate degree and there was neither subjective nor objective evidence of eyestrain.

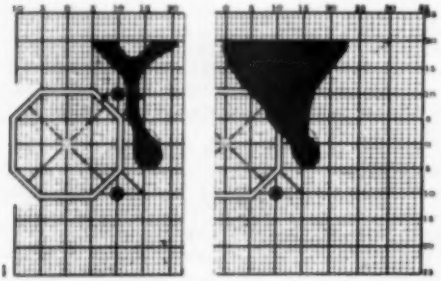

Fig. 1 (Castagno). Showing an increase in the angioscotoma after the local use of homatropine hydrobromide.

The scotoma was mapped according to the technique advocated by Evans.[13] The Evans direct-plotting charts in the campimeter were used with monocular fixation. The diameter of the spherical test object was 0.4 mm. Illumination on the chart was 15 foot-candles. The object was moved from the seeing to the blind region. The blindspot was first outlined and then the angioscotoma arching above the fixation point was mapped.

Procedure

First the subject's angioscotoma was plotted. The blood pressure, size of each pupil, and the vision of each eye were measured. Then one minim of a two-percent saline solution was instilled at the upper limbus by means of eye dropper. This solution was isotonic with a two-percent solution of homatropine hydrobromide and was used as a control. The subject was not aware of this control.

Twenty minutes after instillation of the saline solution, the blood pressure, size of each pupil, and vision were remeasured and a second angioscotoma was mapped. Then one minim of two-percent solution of homatropine hydrobromide was placed at the upper limbus of each eye according to the technique advised by Moncreiff and Scheribel.[14]

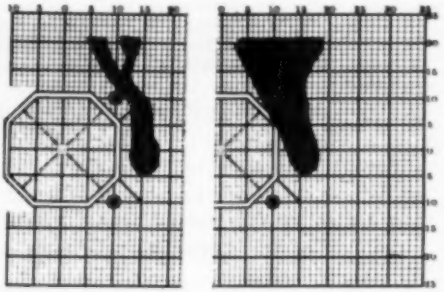

Fig. 2 (Castagno). As is also shown in Figure 1, the increase in the angioscotoma after the local use of homatropine hydrobromide has obliterated the initial bifurcation.

This was repeated at five-minute intervals for a total of five minims in each eye. After each drop, pressure was maintained over the lacrimal sacs for two minutes. The same angioscotomas were then remapped every 15 minutes until no change was noted on three successive mappings.

As a second control it was necessary to employ an artificial two-mm. pupil to find what effect, if any, mydriasis would have as a separate and distinct finding from the action of the medication in relation to the angioscotoma.

There was a dilatation of the normal angioscotoma in each instance (11 eyes of

10 subjects). In no case was the instillation of a two-percent saline solution associated with any detectable effect on the normal angioscotoma nor did the use of the pinhole pupil appear to modify the width of the defect. Pressure on the lacrimal sac alone failed to cause any detectable change in the normal angioscotoma. No change was attributable to the pH of the solution instilled. There was no effect on the angioscotoma of one eye when the fellow eye was dilated with homatropine. No significant change occurred in either the blood pressure or pulse with the use of this drug. Therefore, it seems reasonable to assume that the results as indicated on the charts and graph were not influenced by these factors.

Discussion

Homatropine placed in contact with the cornea diffuses into the anterior chamber. Duke-Elder states that the transference is transcorneal and not an absorption through the perilimbal blood vessels, since such diffusion occurs even when the limbus and conjunctiva are protected.[15] In discussing atropine which is similar, although more prolonged in its action than homatropine, Duke-Elder states that it "dilates the intraocular capillaries increasing their permeability; so far as the vessels to the anterior segment of the uveal tract are concerned, it tends to increase the blood flow since the relaxation of the ciliary muscle through the substance of which the ciliary arteries run removes

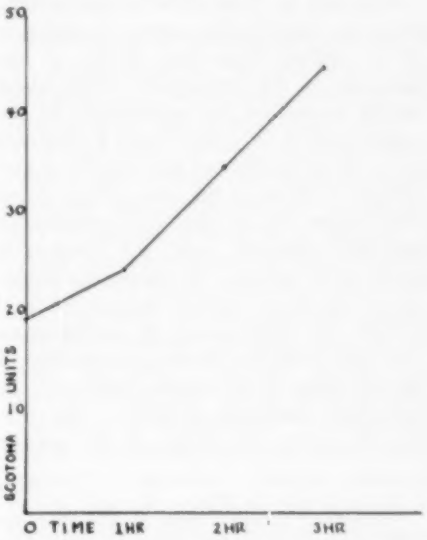

Fig. 3 (Castagno). Average increase in scotoma units in 11 eyes after the local instillation of homatropine.

TABLE 1

Results obtained in study of effect of homatropine hydrobromide on normal angioscotoma

A. Chart of average of results

Number of Eyes	Initial Scotoma Units	Scotoma Units at (in hours)			
		1	1.5	2	3
11	19.4	25.5	29.8	34.7	44.9

B. Chart of typical case

Time of Instillation		Size of Pupil	Scotoma Units	Blood Pressure (in mm. Hg)
Initial	7:00	3 mm.	20	110/78
Saline	7:25	3 mm.	20	110/78
Homatropine started	7:45			
	8:30	7 mm.	25	108/74
	8:45	8 mm.	25	108/74
	9:05	8 mm.	25	110/74
	9:35	8 mm.	40	110/76
	10:00	8 mm.	40	110/76
	10:20	8 mm.	40	110/76

any constriction to their lumen. At the same time the absence of any traction on the choroid allows the vessels of this venous reservoir to collapse, thus tending to encourage stasis. The combined effect thus favors engorgement."[16]

According to Duke-Elder's observations, therefore, homatropine causes a dilatation of the minute intraocular vessels. Is the dilatation of the intraocular vessels alone enough to explain the enlargement of the angioscotoma? In Cases 1 and 2 presented here, the bifurcation of the superior angioscotoma is visible at the first plotting. After homatropine was instilled, the angioscotoma gradually enlarged until the bifurcation could not be plotted. No comparable dilatation of the blood vessels in the fundus could be seen. The dilitation of the angioscotoma after homatropine must be a combination of the dilatation of the blood vessels and the consequent damming of fluid in the perivascular space with edema of the synapse causing a loss of function of the corresponding rods and cones.

Conclusions

In this series of 11 eyes in 10 subjects, the use of a two-percent solution of homatropine hydrobromide instilled locally in the conjunctival sac was apparently associated with a measurable increase in the area of the angioscotoma studied. No consistent change in the blood pressure or pulse was noted during the period of study.

Therefore, it seems reasonable to conclude that conjunctival instillation of two-percent homatropine-hydrobromide solution produces a change of the angioscotoma. In view of this fact, routine angioscotometry should not be done after the administration of homatropine hydrobromide.

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THE HEREDODEGENERATION OF THE MACULA LUTEA*

Diagnostic and differential diagnostic considerations and a histopathologic report

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The heredodegeneration of the macula lutea occupies a special place among the primary tapetoretinal degenerations. It was the last member of this group to be recognized as a definite clinical entity, and it seemingly poses more differential diagnostic problems than any of the others.

A brief explanation of the origin of the term "tapetoretinal" degeneration may not be superfluous. The pioneer investigators of ocular anatomy, histology, and pathology gave Latin names to most of their discoveries, hoping to create a common ground for international understanding. Thus the pigmented epithelium of the retina was also called "tapetum nigrum" (black carpet, black layer), a term by which no reference was intended to the tapetum lucidum occuring only in animals. The tapetum lucidum, located just outside of the choriocapillaris, consists of cellular layers (tapetum celluosum) in the Carnivora, and of fibrillary layers (tapetum fibrosum) in the Herbivora. The pigmented epithelium of the retina lacks pigment over it, permitting the light to fall directly upon it and be reflected. These conditions do not exist in man. When Leber created the expression "tapetoretinal" degeneration for the group of primary lesions of the neuroepithelium (rods or cones) with pigmentary degeneration, which have since been known under this heading, he used the simple and descriptive term tapetum nigrum as its basis, thus including in a single group all primary retinal degenerations, definitely known as such.

A résumé of the most significant clinical characteristics of the heredodegeneration of the macula prior to the discussion of the histopathologic findings will facilitate the interpretation and correlation of both.

In 1920 Behr[1] surveyed the maze of pertinent cases individually reported in the literature, and pointed out that this hereditary or familial disease has a tendency to appear at the crucial times of body development; that is, second dentition, puberty, full adult maturity, and incipient senile involution. He subdivided the large group of primary hereditary macular degeneration correspondingly into the infantile, juvenile, presenile, and senile types. He also mentioned a congenital type based upon Best's[2] hereditary congenital macular affection, which, however, should be kept separate, at least for the present, because nothing is known about the intra-uterine events which lead to it.

In the heredodegenerations of the macula, the pattern of development regarding time of onset, fundus picture, and rate of progress is usually the same in all of the affected members of the same family. It seems that these characteristics are already predetermined in the germ plasm, and that the disease process consists of the premature death of a certain cell system. The duration of the life of a cell or cell system is determined by two factors; namely, the inherited "anlage" and the vital activity of the cells. This law would explain the special vulnerability of the macular cones, which is undoubtedly augmented by the increased vital activity of this region. Added to an inherited anlage it would lead to a premature exhaustion of the vitality of the foveomacular cones at different ages.

* From the Department of Ophthalmology, Northwestern University Medical School, June, 1949.

Fundus pictures of lesions

The fundus picture of the macular lesion varies considerably, often depending on the stage of development at which the lesion is observed, but several distinct forms may be distinguished:

Type I is characterized by inconspicuous, very sharply defined, round or oval areas,

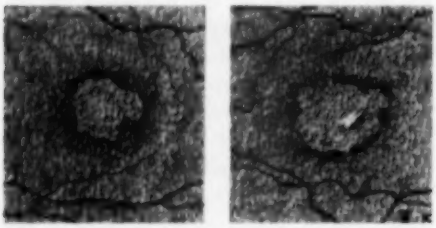

Fig. 1 (Klien). Juvenile heredodegeneration of macula, fundus lesion Type I, in a woman, aged 23 years, with corrected vision: R.E., 0.2+1, J5 with difficulty; L.E., 10/200, no J.

which are only slightly lighter red than the surrounding fundus (fig. 1) and which are therefore, easily overlooked unless brought into sharp focus during ophthalmoscopic observation. They usually become larger and spotted with yellow with advancing age, showing more definite pigmentary disturbances within the lesion and in the adjacent tissue.

Type II shows round yellowish areas over which there is a cystoid bulging of the internal limiting membrane. Families showing this picture are being studied at present by Harold Falls[3] and C. B. McFarland.[4] Falls stated that his impression is that this picture is transitory and that in the later stages it develops the appearance described under the next heading.

Type III. A mixture of small yellowish areas and dustlike or coarser pigment deposits is present. The lesion may be as large as that shown in Figure 2, or it may be quite small and limited to the foveal region. While in some cases it may be the end stage of the lesion described under the second heading, it may have a coarse "pepper and salt" appearance from the beginning.

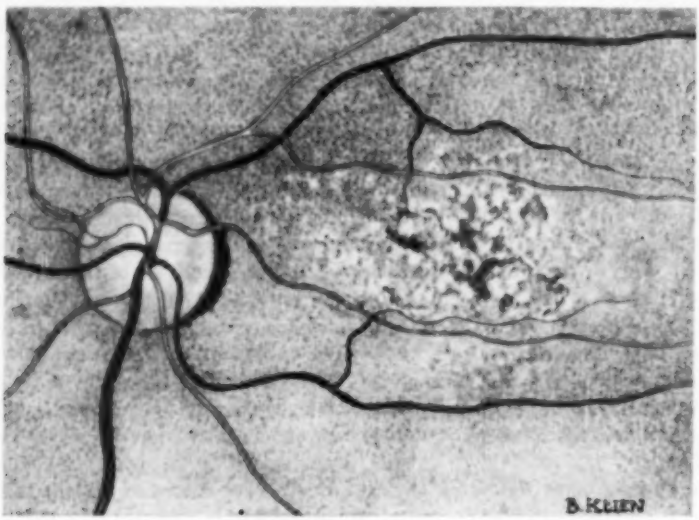

Fig. 2 (Klien). Senile heredodegeneration of macula, fundus lesion Type III, in the left eye of a woman, aged 63 years, with corrected vision: R.E., 0.2; L.E., 0.1.

Comments

In old lesions of any type glistening and drusenlike bodies may appear. Although always bilateral and of almost identical appearance in the two eyes, the lesion is often more advanced in one eye.

The visual disturbance, which has been known to precede the visible changes by more than eight months, commonly appears to be out of proportion to the relatively inconspicuous observable macular involvement. In the early stages of the disease day-blindness is not an infrequent subjective symptom.

Conditions which come into consideration for differential diagnosis vary mainly with the age of the patient. In the younger age-group, familial colloid degeneration of the macula, as described by Doyne[5] and Collins,[6] the nonfamilial colloid degeneration, and the sequelae of central angiospastic retinopathy may have to be ruled out.

In Doyne's colloid degeneration or "honeycomb" chorioiditis, which is also bilateral and hereditary, and in the nonfamilial colloid degeneration, the visual acuity remains good in spite of the striking perifoveal involvement, and declines only during the end-stages of the process. The course of this disease has, therefore, some characterictics which are in marked contrast to the early visual failure of the primary macular heredogeneration, which may precede the clinically visible lesion (Behr,[7] Stargardt[8]).

The residual findings of central angiospastic retinopathy may be unilateral or bilateral, diffuse or circumscribed. They pose a differential diagnostic problem in regard to macular degeneration only when they are bilateral and located in the macula, which is their site of predilection. The fundus picture then often resembles the macular lesion described as Type III. The visual acuity in these cases is apt to be better than might be expected from the appearance of the fundus lesion. Observation of the patient over a period of several years may reveal recurrences of angiospastic attacks, with periods of pronounced impairment of vision followed by some improvement, a course quite different from the slow and permanent deterioration of central vision in the heredodegenerations.

An acute central angiospastic retinopathy (fig. 3) may occasionally simulate the cystic macular lesion described under the second heading (Type II). Involvement of the inner layers of the retina as shown in Figure

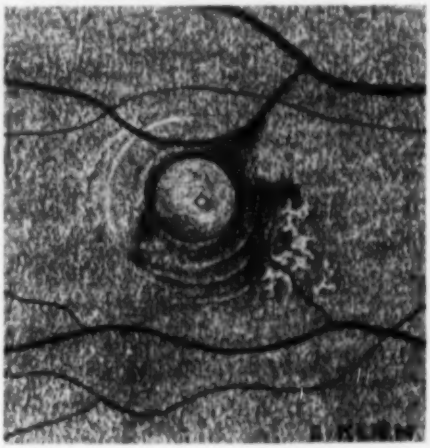

Fig. 3 (Klien). Central angiospastic retinopathy. Cyst in fovea resembling fundus lesion Type II in heredodegeneration of macula. Right eye of a man, aged 35 years, with corrected vision: R.E., 4/200.

3, signs of vasomotor instability, a negative family history regarding tapetoretinal degeneration, the frequent coexistence of some systemic disorder, and long-term observation, eventually lead to the correct diagnosis.

In patients of advanced age, macular degeneration secondary to choroidal sclerosis as described by Friedenwald[9] and Rones[10] has to be differentiated from the heredodegeneration, senile type. In this secondary retinal degeneration, choroidal sclerosis is frequently visible within the confines of the macular lesion after the pigment epithelium has been destroyed (fig. 4), which suggests the correct diagnosis. It is often associated with a peripapillary choroidal atrophy, indicating sclerotic processes in the circulus

vasculosus nervi optici similar to those in the macular region.

Haab's[11] original presentation of the senile macular degeneration dealt with the primary type. He expressed the opinion that it was independent of choroidal sclerosis, but 19 years passed before definite support of this view was obtained by a histopathologic study (Harms[12]).

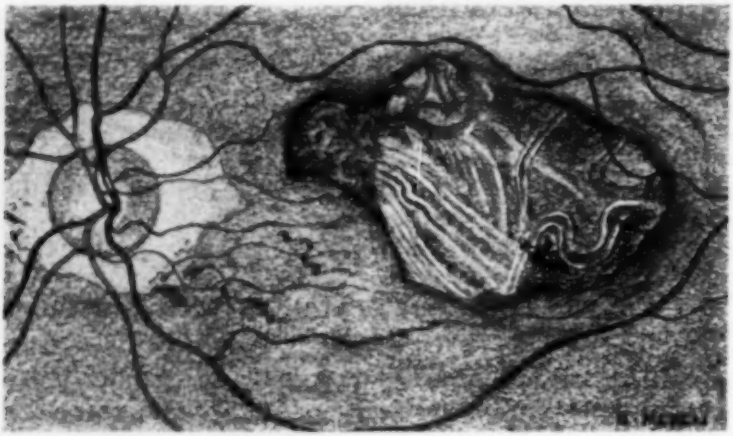

Fig. 4 (Klien). Macular degeneration secondary to choroidal sclerosis. Left eye of a man, aged 73 years, with corrected vision: R.E., 0.2; L.E., 5/200.

Histopathologic reports in literature

Histopathologic reports of heredodegeneration of the macula were made by Nagel,[13] Harms,[12] and Behr.[7] The early reports are characterized by much discussion of the obvious, namely, hyalin excrescences, calcium deposits, and disturbances of the pigment epithelium. An anatomic study in 1858 by Liebreich[14] of the eye of a man, aged 26 years, with colloid bodies in the macula has to be disregarded here because observations on the outer layers of the retina and the choroidal vessels were omitted from the description of the histologic picture.

The first indisputable histologic report of this condition seems to have been made by Nagel in 1875. The term macular degeneration was not used by him, however, and the true nature of the disease was unrecognized at that time. After 10 years of clinical observation, his patient died at the age of 73 years, and he obtained both of her eyes for histologic study. Ophthalmoscopically, the macular areas were occupied by a mixture of light yellowish and pigmented areas with glistening deposits. Histologically there was a large defect of the neuro-epithelium, extensive destruction of the pigment epithelium, and a large number of drusen, some of which contained deposits of calcium carbonate, clinically visible as glistening bodies. The vascular portion of the choroid was normal.

Harms, in 1904, was the first to make a histologic examination of an eye with a clinically diagnosed macular degeneration, which occurred in a man, aged 77 years, reducing his vision to counting fingers at one meter. The histologic findings consisted of disfigurement, migration and clumping of the cells of the pigment epithelium, its detachment from the lamina basalis in places by an albuminous coagulum, and defects in the neuro-epithelium. Harms was the first who definitely rejected alterations of the choroidal vessels as the basis for the lesions of retina

and pigment epithelium, and emphasized the purely retinal nature of the disease.

The most detailed and conclusive histologic report came from Behr,[7] in 1921, one year after his comprehensive clinical study and classification of the heredodegenerations had appeared. In Behr's specimens, the eyes of a man, aged 78 years, the degeneration was in an early stage. Antemortem a typical macular degeneration had been diagnosed, but unfortunately no description of the clinical picture had been made.

In this case the defect in the neuro-epithelium was three times as large as that of the outer nuclear layer, indicating the progression of the degeneration from the outside inward. In the fovea, where all the original cells had perished, there was a fusion of the internal limiting membrane with some remaining cells of the inner nuclear layer, drawn toward the fovea, and with a few displaced nerve fibers. This new membrane was bulging inward, leaving a cystic space between it and the pigment epithelium. The latter was beginning to show slight irregularities. The vessels of the choroid were normal.

Two cases should be mentioned here to which publications erroneously refer as anatomic studies of heredodegeneration of the macula, but which do not belong to this group. Batten and Mayou's[15] case was one of the cerebromacular degeneration, which now is recognized as primarily a lipoid disturbance, associated, for some reasons not yet understood, with either diffuse, or only macular, tapetoretinal degeneration. The second case, studied by Treacher Collins,[6] was a typical honeycomb degeneration (Doyne), whose clinical and histologic picture is dominated by hyalin plaques and excrescences, formed, upon some stimulus, by the pigment epithelium, with secondary degeneration of the neuro-epithelium.

Case report

The following histopathologic study of an eye with heredodegeneration of the macula, the fourth in the literature, can fortunately be presented together with the history of the visual failure and the description of the clinical picture, observed 19 months prior to the enucleation.

Clinical findings

E. B., a woman, aged 60 years, complained of failing vision for the past three years, and an acceleration of this visual deterioration for the last 15 months.

Corrected vision at the time of the first examination was 0.4 in the right eye and 10/200 in the left eye.

The anterior segments of both eyes were normal. Both macular areas were occupied by disciform, irregularly outlined, sharply defined yellowish lesions which were surrounded by spots of pigment proliferations, and a few smaller yellowish red areas. The lesion in the macula of the left eye was larger than that in the right and measured approximately one prism diopter. Aside from slight retinal angiosclerosis, the eyegrounds appeared otherwise normal.

Two months prior to this first examination the patient had received X-ray therapy (5,000 r.) for an incipient squamous cell carcinoma at the inner canthus, where a thin scar remained.

The patient was seen again 19 months later with a recurrence of the carcinoma, which, in the meantime, had invaded the left lids and orbit. The right vision had become reduced during this time 0.2 + 1. The right macular lesion had become larger by confluence with it of several of the adjacent small yellowish red areas. An extensive lagophthalmic keratitis of the cornea of the left eye prevented an accurate test of the vision and a view of the fundus in this eye.

The left globe was obtained by an exenteration of the left orbit and was fixed in formalin.

Histologic findings

The eye was sectioned in a horizontal direction and it proved to be an unusually

well-preserved specimen. There was slight diffuse infiltration with polymorphonuclear leukocytes of the anterior third of the corneal stroma, most pronounced near the inferior and nasal limbus (keratitis e lagophthalmo.) Otherwise the anterior segment was normal.

In the nasal periphery there was marked cystic degeneration of the retina and a scattering of typical senile drusen of the lamina basalis of the choroid. Otherwise also the posterior segment was normal with the exception of the macular lesion to be described:

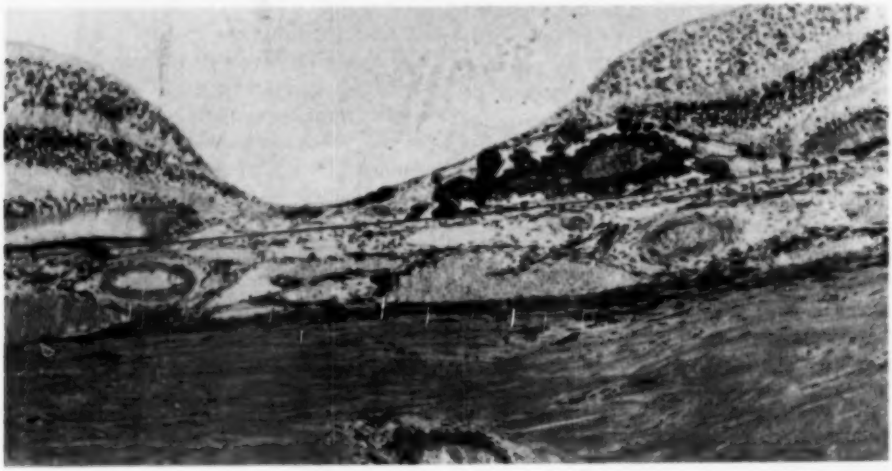

Fig. 5 (Klien). General view of fovea and macula. Complete disappearance of neuroepithelium and pigment epithelium. Cavity temporal to fovea filled with calcium deposits. Bruch's membrane intact, choriocapillaris normal. Mild senile, involutionary type of sclerosis of some of the larger choroidal arteries.

A defect in the outer layers of the macular retina, somewhat eccentrically placed, was the most striking pathologic finding. The neuro-epithelium was completely missing within an area of 1.46 mm. measured horizontally, 0.36 mm. of which was nasal to the fovea. Patchy vacuolization of this layer was present within a diameter of 3.6 mm. There was thinning of the outer nuclear layer within 1.8 mm., and complete absence of it within 0.84 mm. The pigment epithelium was lacking within a diameter of 0.88 mm., 0.24 mm. of this defect was nasal to the fovea. The fovea centralis was occupied by a thin striate membrane and a few nuclei from the inner nuclear layer, which were drawn down the clivus toward the bottom of the fovea. Just temporal to it there was a cystic space, which was filled with a mass of calcium (fig. 5), bound anteriorly by a few nerve fibers and inner nuclei and posteriorly by the lamina basalis of the choroid. Individual pigment-bearing cells or small groups of them were lying here and there adjacent to this cystic space. Henle's fiber layer was narrower than normal, especially on the temporal side. There was a recesssion of all the inner retinal layers from the foveal region, and a barely noticeable reduction of the thickness of the individual layers. The thickness of the retina at the temporal edge of the clivus was 0.296 mm. (normal variations 0.22 to 0.35 mm.), at the nasal edge of the clivus 0.32 (normal variations 0.3 to 0.41 mm.).

More interesting than these obvious macu-

lar alterations were the incipient changes in neuro- and pigment-epithelium of the paracentral macular portions surrounding the central lesion. Defects in the unusually well-preserved neuro-epithelium were easily recognized. They varied in size from 0.008 mm., indicating damage to only a few cells without noticeable changes in the other nuclei, to sizeable holes with incipient rarefaction of the outer nuclear layer.

Alterations of the pigment epithelium were invariably present at the site of these vacuoles. In some places only one pigment cell was leaving the continuity of the epithelium as if attempting to fill the small gap in

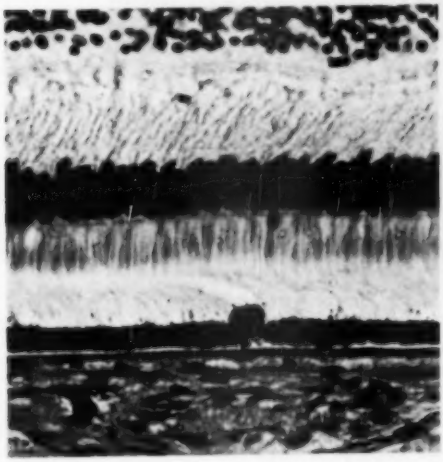

Fig. 6 (Klien). Macular retina near main lesion. Cavity in neuro-epithelium, one cell leaves continuity of pigment epithelium corresponding to location of cavity.

the outer portion of the neuro-epithelium (fig. 6). Movement of the pigment epithelial cells in this direction might be propagated by the physiologic movement of the intracellular granules during vital activity of the cells. At the site of the large vacuoles, the alteration of the pigment epithelium consisted of a detachment comparable to a herniation into the space vacated by the neuro-epithelium. The resulting gap between the detached epithelium and the lamina basalis was filled with either (1) proliferated epithelial cells forming a solid mound of pigment (fig. 7) or (2) by a pale, pinkish staining, finely granular coagulum, giving the ap-

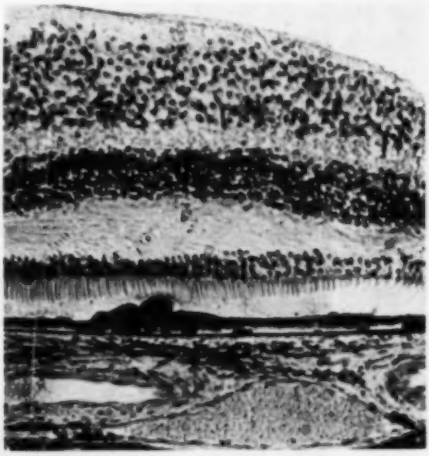

Fig. 7 (Klien). Solid mound of proliferated pigment epithelial cells nasal to fovea.

pearance of a bleb (fig. 8). The pigment content of the cells forming the bleb was often sparse, the cells themselves often flat and elongated.

The lamina basalis of the choroid was intact and of normal appearance everywhere. There were no defects or visible alterations of the chorio-capillaris or the midsized choroidal vessels. There was some thickening of the adventitia in a few of the choroidal arteries, such as is often found as part of the senile involutionary type of angiosclerosis.

There were no signs of inflammation in either retina or choroid in and around the macular lesion.

Comment

The salient features of the histopathologic picture of primary macular degeneration are:

1. The extensive defect of the first retinal

neuron, which is much larger than that of the second and third neuron, and slightly larger than that of the pigment epithelium, indicating the first neuron as the primary seat of the disease.

2. The spotty and perhaps incomplete degeneration of this neuron at an early stage, as indicated by the patchy distribution of the degenerative process in various stages of development in portions of the retina immediately adjoining the main lesion. In the case reported here, some of these areas were visible clinically as small heaps of pigment (histologically as fig. 7), or yellowish red patches, obviously areas with some rarefaction of pigment, as found for instance over flat blebs (fig. 8). Some of these areas were noted in the fellow eye to have merged with the main lesion after the lapse of 19 months.

The clinical features most significant for the interpretation of the histologic findings are the early occurrence of visual disturbances, shown to have preceded visible fundus lesions in several instances, and the day-blindness encountered in the early stages of the disease. The first phenomenon suggests the neuro-epithelium as the primary seat of the disease. The degeneration, although causing visual defects, cannot be observed clinically until secondary pigment changes have set in. The second phenomenon (of day-blindness) was interpreted by Behr as a sign of incomplete degeneration in, nevertheless, severely damaged cells. According to him the visual substances in the inferior grade of neuro- and pigment epithelium become dissociated in normal daylight, a process similar to that occurring in the normal retina after dazzling. The regenerative processes in these eyes are also overstimulated by mere daylight. In twilight dissimilation is reduced but assimilation is not immediately diminished. The resulting accumulation of visual substances makes vision in these eyes more acute in reduced light.

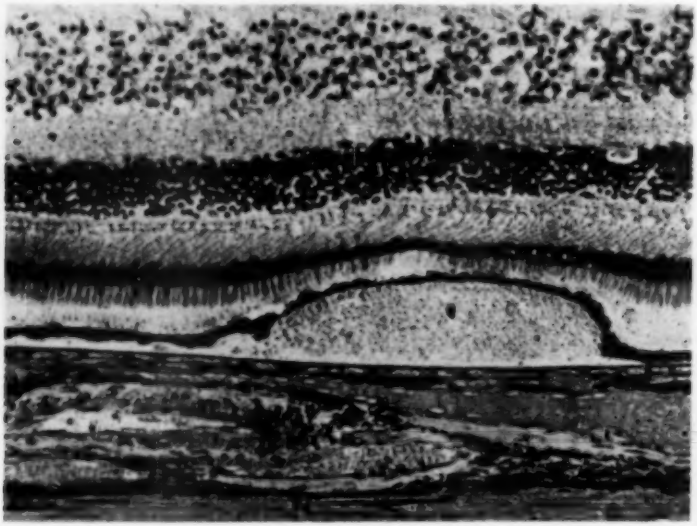

Fig. 8 (Klien). Bleblike detachment of pigment epithelium by serous fluid corresponding to defect in neuro-epithelium, rarefaction of outer nuclear layer.

Detachment of the pigment epithelium by serous fluid, a prominent finding in the histo-

pathologic report of primary macular degeneration by Harms and in the present case, may be encountered in a variety of conditions. In some of them, as in the case of angioid streaks (Klien[16]), it may be due to chronic irritation of the choriocapillaris. In others it appears to be idiopathic (Maumenee[17]). In the primary macular degenerations it may be vicarious, produced from the choriocapillaris by a vacuum between pigment epithelium and Bruch's membrane after the former herniates into the vacuoles within the neuro-epithelium. Stagnating serous fluid is known to favor deposition of calcium, a possible explanation for the frequently mentioned glistening deposits in old tapetoretinal degenerations, which histologic examination has shown to be calcium deposits.

Summary and Conclusions

The primary seat of the pathologic process in heredodegeneration of the macula lutea is in the neuro-epithelium as shown by some histopathologic reports in the literature and one presented here.

Further support is lent to this view by the early subjective symptoms of the disease, which correspond well with the early degenerative changes observable histologically.

Heredodegeneration of the macula, senile type, originally described by Haab as an independent disease primarily affecting the retina, has to be differentiated from senile macular degeneration secondary to marked choroidal angiosclerosis, a condition which appears to be less frequent than the primary degeneration.

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THE PRINCIPLES OF SURGERY ON THE EXTRAOCULAR MUSCLES*

PART I. FUNDAMENTAL PRINCIPLES: CHOICE OF OPERATION IN CONCOMITANT STRABISMUS: HORIZONTAL MUSCLES

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FUNDAMENTAL PRINCIPLES

Operations on the extraocular muscles are, generally speaking, relatively simple. They do not require the dexterity necessary for intraocular surgery. Yet they do present difficulties: many an ophthalmologist prefers the more delicate intraocular surgery to the surgery on extraocular muscles.

These difficulties are difficulties of judgment. They concern such problems as when to operate, what muscle or muscles to tackle, and what type of operation to choose. The diagnostic examination in the office and the therapeutic conclusions drawn therefrom largely determine whether the operation will be a success or a failure.

The time has long since past when affections of the ocular motility were considered to be purely mechanical anomalies. It is generally recognized that these affections represent a complex dysfunction of the whole neuromuscular system of the eyes. A rational treatment of heterophoria and heterotropia has to take this into account.

Generally speaking, the etiologic factors directly responsible for heterophorias and heterotropias are (1) innervational factors, (2) fusional factors, and (3) noninnervational factors.

The innervational factors are, in cases of heterophorias and heterotropias, the factors connected with the function of accommodation, and, through accommodation, with the refractive error present. In paralytic strabismus the innervational factors relate the imbalance of the innervations to the various groups of muscles. In both concomitant and paralytic strabismus disturbances on various levels of the central nervous system may be present.

The fusional factors are concerned with the binocular coöperation of the eyes, not only with the presence or absence of sensory fusion, but with the whole sensory and sensorimotor response of the patient to binocular stimulation.

The noninnervational factors include mechanical factors such as the size and attachment of the ocular muscles, the elastic predominance of one group of muscles or an insufficiency of the antagonistic group; irregularities in the size of the orbits or the globes, the volume and quality of the retrobulbar tissue, anomalies of the ligaments, and so on.

As I have stated, a rational treatment has to take into account all these factors and must be directed against them. The examination of the patient discloses, insofar as this is possible, which of these factors are predominant in the individual case and determines the therapeutic course to be taken.

We have at our disposal nonsurgical and surgical means to correct anomalies of the neuromuscular apparatus of the eyes.

The first and foremost principle regarding the surgical procedures is that they can only change the mechanical conditions by changing the position of the globe in the orbit and by changing the effectiveness of the extraocular muscles. But such procedures can never directly affect the innervations reaching the eyes. These can only be indirectly affected by surgery when the innervational and sensory conditions adapt themselves to the newly created anatomic and mechanical conditions.

On the other hand, a change in the innervational factors may well influence the

* Read at the meeting of the Cincinnati Ophthalmologic Club, October 8, 1948.

position of the eyes. Thus, when a child with accommodative covergent strabismus puts on glasses, the eyes may become straight. Or when a person with divergent strabismus has learned—spontaneously or by fusion training—how to keep his eyes straight, they remain so as long as the patient maintains the compensatory convergence effort. But neither glasses nor fusion training can effect a lasting change in the mechanical and anatomic situation of the globe. As soon as the special innervational conditions cease to exist —as when the child removes the glasses or when the convergence effort is relaxed—the faulty relative position of the eyes returns.

These may seem trite statements, yet these fundamental facts are not always kept clearly in mind. By disregarding them, many an operation has been performed which was unnecessary or actually harmful, and confusion has been created as to indications and choice of operation. And by disregarding them, many a patient has been subjected to unduly prolonged and in the final result, unsatisfactory orthoptic treatment, when a combination of surgery and orthoptics might have hastened the recovery or even made a recovery possible, when there was none.

To repeat then, surgery can directly influence only the mechanical conditions—the effectiveness of the muscles and the position of the eyeballs in the orbit. Measures directed toward improving innervational conditions can only correct the position of the eyes to a certain extent and do not produce a lasting change in the mechanical conditions.

Choice of operation in concomitant strabismus—Horizontal muscles

Armed with a knowledge of these fundamental principles, we shall now consider the surgical treatment of concomitant strabismus.

After the decision has been reached that a patient with concomitant strabismus should be operated upon, the question arises which muscle or muscles should be operated upon and what type of operation should be performed.

In principle there are only two types of operations on the extraocular muscles: the action of a muscle is either strengthened or weakened by the surgical intervention. The question of the choice of surgery can, therefore, be put in this way: Should the action of a certain muscle be weakened or should the action of the antagonist be strengthened and how much should it be strengthened or weakened? In other words, what is the criterion on which to base our choice of operation?

There is a widespread teaching according to which this decision should largely be based on the faculty of the eyes to converge or diverge. A patient with either convergent or divergent strabismus may show normal, excessive, or defective convergence. If the eyes assume a relatively more divergent position for near than for distance, convergence is defective; if they assume a relatively more divergent position for distance than for near, there is said to be a divergence excess. Similarly, there are said to be a convergence excess and a divergence insufficiency. Elaborate tables have been constructed which advise what type of operation to perform in these different cases, taking into account also the magnitude of the angle of squint.

All these rules, in the last analysis, come down to this: that one should not weaken the internal rectus muscles, if convergence is deficient, for fear of increasing the deficiency, but that they may be weakened, if convergence is normal or excessive. Similarly, if there is a divergence excess, one should rather weaken the external rectus muscles than strengthen the internal rectus muscles, and so on.

I believe it to be a fallacy to base the choice of operation on the behavior of convergence and divergence. Remember the fundamental principle that operations cannot influence directly the innervational condi-

tions. Now, convergence and divergence are innervational factors. We are, indeed, very much interested in their behavior in our patients, but not from the point of view of surgical procedure.

It must be remembered that the internal rectus muscle has a twofold action. In lateroversion it is synergistic with the external rectus of the opposite eye. In convergence it is synergistic with the internal rectus of the opposite eye. The two movements, lateroversion and convergence, are different in many respects. Lateroversion, as all versions, is a quick, tetanic movement. Convergence, as all vergences, is a slow shift in the tonic balance of the extraocular muscles.

Lateroversion and convergence have a different representation in the central nervous system; they arise independently. As is well known, there may be a functional or organic paralysis of convergence in a patient whose lateroversions are perfectly normal. And it is also known that in cases of supranuclear paralysis of the internal rectus muscle in which the patient is entirely unable to perform a movement of lateroversion, the convergence may be perfectly intact.

The fear that a convergence insufficiency will be created or exaggerated by weakening of the action of the internal rectus muscles rests on the old misconception that neuromuscular anomalies are caused by deficient "strength" of the ocular muscles themselves. Most ophthalmologists will today admit that this is a misconception, but it nevertheless crops up time and again in more or less disguised forms.

Actually, the internal rectus muscles are, with very few exceptions, always able to perform the necessary contraction to cause the eyes to converge maximally. Witness the fact that even in cases of marked convergence insufficiency the eyeballs can nevertheless be adducted normally or even excessively. What is lacking in convergence insufficiency is the impulse, not the strength of the muscle.

To be sure, if the internal rectus muscles are recessed behind the center of rotation of the eye and a mechanical paresis is created, convergence will suffer together with the action of the muscle in lateroversion. But to do this is in any event a mistake, no matter what criterion is chosen for the operation.

A properly executed operation, irrespective of the type, will result in a change of the position of the eyes in the orbit so that their relative position is now correct.

Take a case of divergent strabismus. When the patient is rested and in good physical condition, he may be able to keep his eyes parallel for distance, and even converge pretty well at near for a certain length of time by a more or less conscious effort of convergence. He has trained his convergence which is actually quite good, even if his near point is somewhat remote.

Now, if his eyes are straightened by surgery, he will not have to exert any convergence effort for distance. If he exerts the full effort of convergence of which he is capable, his near point will now be closer than prior to the operation and possibly even excessive.

One advantage of the operation is that he does not have to exert for the same visual distance as much convergence as prior to the operation. This result is achieved by changing the relative position of the eyes. Whether this was done by surgery on the internal or external rectus muscles is not essential, always assuming that there was no gross technical error in the operation.

The innervational factor of convergence faculty is not influenced directly by changing the position of the eyes. In time the correct position of the eyes may exert an influence on the innervational factors, but this again is dependent on the position of the eyes, not on the way by which the new position was achieved.

Now, if the behavior of convergence is not the proper criterion, on what shall we base the choice of the operation? The answer is that we should base it on the behavior of

the versions or the excursions of the eyeballs. In the vast majority of cases of concomitant strabismus we find that the rotations are abnormal. In convergent strabismus the adduction of the eyes is usually excessive; the abduction may be deficient. And we observe again that this excess or deficiency does not necessarily run parallel to an excess or deficiency of convergence. Thus there may be, for instance, a divergent strabismus with excellent convergence near point, but very poor adduction; or a convergent strabismus with enormous excess of adduction, yet deficient near point of convergence.

The goal in the surgery on the extraocular muscles should be the normalization of the excursions of the eyes. If this is achieved, the angle of squint will be automatically reduced.

If there is an excess of a certain movement, the action of the muscle governing that movement should be weakened; if there is a deficiency, a strengthening of the action of the corresponding muscle is indicated. If both excess of movement in one direction and deficiency in the opposite direction are present, two muscles may be operated upon, weakening the stronger acting and strengthening the one deficient in action.

In the latter case some caution is, however, necessary. I have frequently observed, for instance in convergent strabismus, that there was a marked excess of adduction, accompanied by what appeared to be a mild deficiency of abduction. After weakening the action of the internal rectus muscle and normalizing the adduction, the abduction also became normal. I explain this on the basis of reciprocal innervation. The excessive action of the internal rectus muscle, noted preoperatively, produced by reciprocal innervation a slight deficiency of abduction which became automatically normalized when the excess of adduction was removed.

When there is neither an excess nor a deficiency in the excursions of the eyes, it is advisable to rely on strengthening operations rather than on weakening operations, since a weakening operation in such a situation is likely to produce a postoperative deficiency of the action of the weakened muscle with resulting restriction in its field of action.

In esotropia there is almost always an excess of adduction present. The operation of choice is, therefore, as a rule, a recession of one or both internal rectus muscles to which a resection of the external rectus muscles may be added, if the angle of squint is very large.

In exotropia, whether there is a deficiency of adduction or not, a resection of the internal rectus muscles (with or without advancement) is the operation of choice. To increase the effectiveness of the resections, recessions of the external rectus muscles may be added if the angle of squint is large. Recessions of these muscles alone are not advisable; if they are to be effective at all the muscles must be set so far back that they will produce a deficiency of abduction.

Once the type of operation is decided upon the question arises: how much, in millimeters, should the muscle be recessed or resected? I always have great difficulties in giving an answer to this question which I am constantly asked.

All general rules about the dosage of muscle operations on the eyes are misleading. Most physicians have a superstitious belief in figures and, more especially, in figures with many decimal points. The physicist and chemist know that the number of valid decimal points is determined by the accuracy of the method employed. Adding on paper a few decimal points does not make the method more accurate; it results in spurious, pretended accuracy.

Operations on the ocular muscles are extremely coarse procedures. The effect of the operations depends by no means only on the actual amount of change in the distance of the insertion from the limbus. It also depends on the conditions existing prior to the intervention, on the greater or lesser thoroughness with which the muscle was freed, and last but not least, on the fine regulating

neural mechanisms which govern the movements of the eyes.

Valid directions for the dosage of the operations can only be given in general terms. Nowhere is experience more necessary than here.

In general, recessions are more effective than resections; also, their effect is more lasting—that is, the immediate postoperative result represents more or less the end result. It depends on how excessive the movement was preoperatively, how much one may recess, and how great the effect will be. The greater the excess, the further one may recess. Also, the greater the excess, the greater is the effect on the angle of squint.

This fact explains why recessions of the internal rectus muscle are more effective than recessions of the external rectus muscle, since an excess of abduction is never anywhere near as large as the average excess of adduction. In the ordinary run of cases of esotropia, I figure that a recession of one internal rectus muscle will reduce the angle of squint by about one half.

The danger of all recession operations is that they may lead, immediately or in time, to an overeffect. As a result a former convergent strabismus may be transformed into a divergent strabismus. This is a most unfortunate happening for everybody concerned, but I believe that it is avoidable.

First of all, a muscle should never be recessed so far as to lose, for mechanical reasons, its power to act; that is, it should not be set back beyond the equatorial plane of the eye. On the other hand, very small recessions, of 1.5 or 2 mm., are rather pointless. They can only be recommended when one wishes temporarily to reinforce the effect of a resection of the antagonist. In general, recessions of the internal rectus of 5 to 6 mm. are most satisfactory.

Furthermore, I strongly advise against recessing both internal rectus muscles at the same time. In my hands this has invariably led to an overeffect. I am aware that there are excellent surgeons of experience who do not hesitate to recess both internal rectus muscles in one sitting. I must say, however, that I have seen quite a number of cases of postoperative divergence follow operations performed in this way by others than myself.

The most important test as to whether a recession was successful or not and the surest safeguard against postoperative divergence is a check of the excursions of the eyes. If the adduction of the operated eye is still excessive, the recession was not extensive enough. If the adduction is deficient, this is always a danger sign. The patient should be closely watched and, if necessary, the internal rectus should be reattached closer to its original insertion before a disfiguring strabismus occurs.

I wish to mention here briefly the controversy of tenotomy versus recession. To sever simply the insertion of a horizontal muscle is today considered to be very bad practice indeed and entirely to be condemned. As so often happens, a very good point—the securing of the tendon of the muscle to the sclera—has been overstressed to the extent that essential features are overlooked.

If the tenotomy is performed as it should be, by opening the conjunctiva and severing the tendon only at the scleral insertion without freeing the connections between the muscle and Tenon's capsule, and if in addition a safeguarding suture is placed through the muscle and loosely tied, permitting a pulling forward of the muscle if it should have slipped back too far, then this very simple operation, which requires no binocular bandage and no postoperative care to speak of, has to my mind a very definite place in the surgical armamentarium.

I believe that it is in some respects preferable to recession operations. Aside from its simplicity, one of the main reasons is that the muscle itself is not touched and that its sheath and all the connections with Tenon's capsule remain undisturbed. This is physiologically very desirable. To be sure, one can-

not graduate this operation as exactly as the recession operation. But the exact graduation of the recession operations, too, is to my mind rather questionable, as I have pointed out.

However, this does not mean that I belittle recession operations. Particularly when one operates on vertical muscles, and in combined operations on the horizontal muscles, they are indispensable.

Resections are, on the whole, less effective than recessions or tenotomies and—this is even more important—their effect diminishes in time. Approximately 4 to 6 months after the operation, the final result is established. It is, therefore, desirable to aim at an immediate overeffect after resection operations to obtain the desired end-result. This holds true particularly for operations for divergent strabismus in which the internal rectus muscles are resected. Here it is desirable to have immediately after the operation on overeffect, an esotropia. This reduces itself very soon and the eyes become invariably either parallel or return to a more or less exotropic position.

Resection operations are, in general, of no avail unless at least 10 to 12 mm. of the muscle is resected. The effect of the resection operations can be considerably increased by advancing the insertion of the resected muscle or by combining it with a recession of the antagonist.

In contradistinction to the situation in recessions, I believe it to be good practice to resect at the same session both homonymous muscles—that is, both internal rectus muscles or both external rectus muscles. In divergent strabismus, whether there is a deficiency of adduction or not, this is almost invariably the operation of choice and it is very effective in alternating convergent strabismus without excess of adduction.

The reason why I advocate such procedures is that I believe that the operations should be, insofar as possible, symmetrically divided between the two eyes. If too strenuous an attempt is made to remove the angle of squint by operating on one eye only, frequently there are created artificial anomalies of the rotations. The unoperated eye retains its abnormal excursions. All this produces an imbalance of the ocular movements which may assume the form of an actual, if slight, paresis with a primary and secondary angle of squint.

It is for this reason, also, that I favor strongly multiple operations in the majority of cases of concomitant strabismus. Normal excursions in both eyes cannot be established by operating on one eye only, as has just been pointed out. If both eyes are operated upon in one session, there is a real danger of an overeffect, particularly in convergent strabismus. The best scheme seems to me to be to operate first on the habitually nonfixating eye and some time later, after the result of the first operation has been established, to operate on the other eye. This permits one to determine the best procedure for the second operation. Occasionally a third operation may prove necessary.

The disadvantage of having to give more than one anesthesia to the child is overbalanced by the advantages of the multiple operations. If the situation is clearly explained to the patient or the child's parents, there will hardly ever be an insuperable objection to this procedure.

A word must be said now about the age at which a patient should be operated upon for concomitant strabismus.

I think that today we are all agreed that it is quite unnecessary to wait until a child is 12 or 14 years of age before operation. The danger of an overeffect after a lapse of years is nil if the operations are properly performed. Indeed, it is advisable to operate on the children at an early age, if a functional cure is the goal. We all know how much easier it is for a younger child to acquire new visual habits than for an older one.

After the refractive correction has been

worn by the child for a few months, after the visual acuity has been established and, if necessary, occlusion and other preliminary orthoptic procedures carried out, then it is time to operate. The child is by then usually 4 to 5 years of age or a little older. In general, I favor straightening the eyes before the child enters the first grade, if for no other reason than to avoid the bad effect which being taunted by their schoolmates because of their eyes has on some sensitive children. Such taunting occasionally has a devastating effect on the whole life of a youngster.

As a rule, I do not operate on a child under 3 to 3½ years, but there are some rare cases in which one may operate earlier. Those are cases in which the angle of convergent strabismus is very high and the refractive error low (usually based on inveterate external rectus palsies) and the young mother is very unhappy about the appearance of her child. Children with ocular torticollis may also be operated earlier.

This is not the place to enter into a discussion of the sensory reactions of a patient with concomitant strabismus. There is, however, one point which I should like to make. It is my belief that abnormalities in the sensory reactions are the consequence, not the cause, of the abnormal position of the eyes. A study of the binocular coöperation of a patient with concomitant strabismus is of great interest if we aim at the restoration of function. From the point of view of surgery it is of little or no interest.

It is often claimed that an anomalous retinal correspondence should be cured before surgery is undertaken, since there is the danger that the eyes may return to their preoperative position under the influence of the old anomalous correspondence. I have never been able to convince myself of this in all the cases which I have seen.

Whenever an operation was not successful, I have always found a good reason for it by testing the rotations which were not normalized. If the rotations were normal, no amount of anomalous correspondence has ever changed the position of the eyes in any of the cases which have come to my attention.

I shall consider now a few specific examples of horizontal heterotropias and make suggestions regarding surgery, but let me emphasize again that these are not hard and fast rules.

A. Convergent strabismus

a. Monocular with high amblyopia and high angle of squint. Recession of the internal rectus combined with resection of the external rectus of the deviated eye are indicated. In these cases a maximum effect should be aimed at, since these eyes tend to return to their convergent position. If necessary, surgery on the fixating eye (recession of the internal rectus) may be added later.

b. Monocular strabismus with amblyopia but good fixation of the deviated eye (vision 20/30 to 20/70). This group comprises the bulk of the cases. Usually there is a marked excess of adduction in both eyes, frequently more pronounced in the deviated eye. My routine is to recess the internal rectus of the deviated eye first; if the angle of squint is very high (30° or over), it is advisable to add a resection of the external rectus. After this operation the adduction in the deviated eye should be normalized.

Since the nonoperated eye still shows an excessive adduction, one finds now almost always in the cover test that the angle of squint is greater when that eye assumes fixation. When the result of the first operation is thoroughly established (that is, not before 6 to 8 weeks), the second eye can be operated upon. In accordance with the findings a recession or a combined operation is performed. Finally, if only recessions have been done and if there is a small residue of convergent strabismus, a resection of the external rectus on the deviated eye, or on both external rectus muscles, is added.

c. Alternating convergent strabismus. The procedures are essentially the same as in (b). But one finds often that in these cases the adduction is less excessive than in monocular convergent strabismus and I am, therefore, inclined to rely here more on the resection than on the recession. The less marked the excess of adduction, the more weight is given to the resection. If there is no excess of adduction, as occasionally happens, I do no recession at all, even if the angle is rather large, but an extensive bilateral resection, aiming at a slight immediate postoperative overeffect.

B. Divergent strabismus

a. Strictly monocular (with or without amblyopia). Resection of one or both internal rectus muscles should be combined with recession of the external rectus muscle of the deviated eye.

b. Alternating divergent strabismus. Whether there is deficient adduction or not, the operation of choice is a bilateral resection of the internal rectus muscles. If the angle of squint is large, it may be combined with recessions of the external rectus muscles.

In general, it is more difficult to obtain a satisfactory end-result in exotropia than in esotropia. It is, therefore, advisable to produce a slight overeffect after the operation, but this overeffect should be the result of the resections rather than the recessions.

(To be concluded)

THE IRRITATING EFFECTS OF MALEIC ACID AND OF MALEIC ANHYDRIDE UPON THE EYES OF RABBITS*

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In an industrial process involving exposure of workmen to the fumes of maleic acid, it became of interest to ascertain whether such exposure might involve risk of irritation to the eyes. Contact with fumes or solutions of maleic anhydride is reported to have caused distressing but not serious symptoms in man.[3] Eight men were affected, displaying such signs and symptoms as painful conjunctivitis, vesicular dermatitis, and upper respiratory irritation with cough.

There have been no controlled experiments in animals on the irritating properties of maleic acid or maleic anhydride, and there is little information in the literature on the toxicity of these compounds. Maleic acid is relatively nontoxic parenterally or by mouth. Dye and others[1] observed no effect on rats injected daily with maleic acid from the seventh to the 60th day of age with doses starting at 0.5 mg. and increasing to 2 mg. by the fourth week of age, nor on chick embryos given 0.05 mg. per embryo on the 10th day of incubation. Fitzhugh and Nelson[2] found no effect on growth of rats fed maleic acid at a level of 0.5 percent in the diet for one year, though there was some increase in mortality during the second year. When 1.0 and 1.5 percent were fed, retardation in growth was evident after one year of feeding, and increased mortality after 18 months.

Experimental

A. Solutions

The effect of solutions of maleic acid and maleic anhydride was tested in the eyes of rabbits by filling the conjunctival sac of the right eye with solution, and allowing it to remain in contact with the eye for two minutes, then allowing it to drain out. Two

* From the Merck Institute for Therapeutic Research.

rabbits were used for testing each of the following solutions: maleic acid (1 percent and 5 percent) maleic anhydride (1 percent and 5 percent).

In the animals receiving one-percent solutions, there was cloudiness of the cornea, hyperemia of the conjunctiva, and edema of the nictitating membrane within a few minutes after application. This condition lasted throughout the day, but the eyes appeared to be normal the next morning. In the animals to which five-percent solution was administered, the irritation was qualitatively similar, but more intense, involved the iris as well as the cornea, and did not disappear until the sixth or seventh day.

B. Powder

For these tests, the material was ground in a mortar to a fine powder, and a minute amount was placed in the right eye, and allowed to be washed away by tears. Two rabbits received maleic acid, and two received maleic anhydride.

In all cases, there was immediate clouding of the cornea. The animals behaved as though they were in distress, so presumably the application was painful.

Twenty-four hours after maleic acid, there was apparent sloughing of the superficial layers of the cornea. After two days, one rabbit had a white cloudy spot about two mm. in diameter on the cornea, which did not stain with fluorescein. In all of the animals, edema, inflammation, and cloudiness of the cornea were present, but it was more marked in those receiving maleic anhydride. There was a profuse whitish discharge from the affected eyes. After three days, there was in each eye treated with the anhydride a corneal ulcer which stained with fluorescein.

Neither the solutions nor the powder produced mydriasis or miosis, nor was the pupillary light reflex affected. No sign of systemic effect was noted in the animals, except dilatation of the ear vessels in one rabbit about an hour after instillation of one-percent maleic acid.

The eyes treated with maleic-acid powder returned to normal within a few days. On the other hand, the affected areas on the corneas treated with maleic-anhydride powder were white, opaque, and well vascularized seven weeks after application of the drug. There were distinct blood vessels entering the clouded area from the periphery of the cornea, which branched to form a network over the injured region. The areas involved, however, no longer stained when one-percent fluorescein solution was dropped into the eye. These areas were near the center of the cornea, and undoubtedly made normal vision impossible in the affected eye.

Conclusion

Maleic acid and its anhydride, tested by application of solutions and of powdered substance to the eyes of rabbits, proved to be extremely irritating. A minute amount of powdered maleic anhydride produced long lasting damage with vascularization of the cornea.

Merck Institute.

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THE RATE OF OUTFLOW OF FLUID FROM THE EYE UNDER INCREASED PRESSURE*

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When a tonometer is placed upon the eye, the cornea is indented and the intraocular pressure is raised (tonometric pressure). If the tonometer is kept upon the eye, fluid is slowly expressed from the eye and the scale indicator falls. Friedenwald[1, 2] has determined the volume of the corneal indentation and the tonometric pressure for each scale reading with each plunger load of the Schiøtz tonometer. Thus, it is possible to state how much fluid has left the eye at a given pressure during a given time. A table giving the volume of the corneal indentation and the intraocular pressure during tonometry corresponding to different scale readings and plunger loads was furnished us by Dr. Friedenwald. This table was derived from his most recent and, as yet, unpublished study on the calibration of tonometers. In abbreviated form his data are presented with his permission as Table 1 of this paper.

We have attempted to measure the relationship between pressure and rate of outflow of fluid (a) in normal eyes, (b) in normal eyes treated with drugs, and (c) in glaucomatous eyes.

METHOD

The subject is prepared as for ordinary tonometry, the eye being anesthetized with 3 or 4 instillations of 0.5-percent pontocaine. A preliminary reading is made with the tonometer and two minutes are allowed to elapse. The tonometer is then loaded with the desired plunger load and is replaced upon the eye and kept there. Readings are recorded initially and every 10 seconds for a total of two minutes (13 readings). The scale readings are then translated into corneal-indentation volumes and tonometric pressures (table 1). The volumes are plotted against time and a line is drawn through the points. The 0- and 120-second ordinates of the line are taken as the corrected volumes. The initial corrected volume is subtracted from the final, the difference being the volume of fluid lost from the eye in two minutes. The initial and final corrected tonometric pressures are averaged, giving the average pressure in the eye during the time of measured fluid loss.

EXAMPLE

Subject R. A. M.

(L.E. Experiment No. 233)

Preliminary reading (5.5 gm. wt.) = 7.0 scale units

Compression series (7.5 gm. wt.)

Time (seconds)	Tonometer Scale Reading	Volume Displacement (mm.³)
0	10.0	19.9
10	10.0	19.9
20	10.25	20.5
30	10.50	21.1
40	11.0	22.3
50	11.0	22.3
60	11.25	22.9
70	11.0	22.3
80	11.5	23.5
90	11.75	24.2
100	12.0	24.8
110	12.0	24.8
120	12.25	25.5

Figure 1 is a plot of the volumes against time. Using the line as a correction:

	Volume Displacement (mm.³)		Tonometric Pressure (mm. Hg)
Initial	19.7		32.7
Final	25.5		29.1
Difference	5.8	Average	30.9

This shows that 5.8 mm.³ have left the

* From the Wilmer Ophthalmological Institute of The Johns Hopkins University and Hospital. This work was supported in part by the Chalfant Fund.

TABLE 1*

TONOMETRIC DATA USED IN EXPERIMENTS ON RATE OF OUTFLOW OF FLUID FROM EYES UNDER PRESSURE

	5.5		7.5		10		15	
Scale Reading	Tonometric Pressure	Volume Displaced	Tonometric Pressure	Volume Displaced	Tonometric Pressure	Volume Displaced	Tonometric Pressure	Volume Displaced
	mm. Hg	cu. mm.	mm. Hg	cu. mm.	mm. Hg	cu. mm.	mm. Hg	cu. mm.
0.0	51.3	5.29	70.0	3.80	93.3	2.80	140.0	1.90
0.5	48.6	5.91	66.2	4.27	88.3	3.18	132.4	2.18
1.0	46.1	6.58	62.8	4.79	83.8	3.59	125.6	2.49
1.5	43.8	7.28	59.7	5.34	79.7	4.02	191.5	2.82
2.0	41.8	8.01	57.0	5.93	75.9	4.49	113.9	3.18
2.5	39.9	8.78	54.4	6.54	72.6	4.98	108.8	3.57
3.0	38.2	9.58	52.1	7.19	69.5	5.51	104.2	3.99
3.5	36.7	10.4	50.0	7.88	66.6	6.06	99.9	4.43
4.0	35.2	11.3	48.0	8.59	64.0	6.65	96.0	4.90
4.5	33.9	12.2	46.2	9.34	61.6	7.27	92.4	5.40
5.0	32.6	13.2	44.5	10.1	59.4	7.91	89.0	5.93
5.5	31.5	14.1	43.0	10.9	57.3	8.59	85.9	6.49
6.0	30.4	15.3	41.5	11.8	55.3	9.30	83.0	7.08
6.5	29.4	16.2	40.1	12.7	53.5	10.0	80.3	7.70
7.0	28.5	17.3	38.9	13.6	51.8	10.8	77.7	8.35
7.5	27.6	18.4	37.7	14.6	50.2	11.6	75.3	9.04
8.0	26.8	19.6	36.5	15.6	48.7	12.5	73.1	9.76
8.5	26.0	20.8	35.5	16.6	47.3	13.3	71.0	10.5
9.0	25.3	22.0	34.5	17.7	46.0	14.2	69.0	11.3
9.5	24.6	23.3	33.5	18.8	44.7	15.3	67.1	12.1
10.0	23.9	24.6	32.6	19.9	43.5	16.2	65.3	13.0
10.5	23.3	26.0	31.8	21.1	42.4	17.2	63.6	13.9
11.0	22.7	27.3	31.0	22.3	41.3	18.2	62.0	14.8
11.5	22.2	28.7	30.2	23.5	40.3	19.3	60.4	15.8
12.0	21.6	30.2	29.5	24.8	39.3	20.4	59.0	16.8
12.5	21.1	31.7	28.8	26.1	38.4	21.6	57.6	17.8
13.0	20.6	33.2	28.1	27.5	37.5	22.7	56.3	18.9
13.5	20.2	34.8	27.5	28.9	36.7	24.0	55.0	20.0
14.0	19.7	36.4	26.9	30.3	35.9	25.2	53.8	21.1
14.5	19.3	38.0	26.3	31.8	35.1	26.5	52.6	22.3
15.0	18.9	39.6	25.8	33.3	34.4	27.8	51.5	23.6
15.5	18.5	41.4	25.2	34.8	33.6	29.2	50.5	24.8
16.0	18.1	43.1	24.7	36.4	33.0	30.6	49.4	26.1
16.5	17.8	44.9	24.2	38.0	32.3	32.1	48.5	27.5
17.0	17.4	46.7	23.8	39.7	31.7	33.5	47.5	28.9
17.5	17.1	48.5	23.3	41.3	31.1	35.1	46.6	30.3
18.0	16.8	50.4	22.9	43.1	30.5	36.6	45.7	31.8
18.5	16.5	52.3	22.5	44.9	29.9	38.2	44.9	33.3
19.0	16.2	54.3	22.1	46.8	29.4	39.8	44.1	34.9
19.5	15.9	56.3	21.7	48.5	28.9	41.5	43.3	36.5
20.0	15.6	58.3	21.1	50.4	28.4	43.2	42.6	38.1

* This table was derived from the most recent tonometric studies of Dr. Jonas S. Friedenwald.

eye in two minutes or 2.9 mm.[3] per minute, at an average pressure of 30.9 mm. Hg. It is seen that the actual tonometric pressure change during this time is only 3.6 mm. Hg, and the use of an average pressure does not introduce a serious error.

A shorter method is to use the initial and final uncorrected figures. The error of such a procedure is usually not large.

It is seen from the experimental data and the graph that the exit of the fluid is not a smooth process, but is somewhat variable in rate. In order to study this phenomenon more closely we photographed the meter of a Mueller electronic tonometer on moving bromide paper (fig. 2). A diagram of the apparatus for this photographic recording is shown in Figure 3.

The tonometers used were: one Sklar-model, certified Schiøtz tonometer, and two

different Mueller certified Schiøtz electronic tonometers.*

As a rule only one determination per day was made on each eye investigated. Readings were discontinued at Scale 18 in order to avoid striking the lens. All readings were made by us.

Results

Normal eyes

Figure 4 represents the results of 130 measurements on 63 normal eyes. Boundary lines were drawn around the scatter of points on the graph (with the exclusion of one point) to serve as "limits of normal" for reference in other plots.

Figure 5 gives the results of 21 measurements on one normal eye (the left eye of Subject R. A. M.). Some trials with the 15-gm. weight gave so rapid a rate of flow at so low an initial pressure that sufficient data could not be collected for computation. Similar sets of results were obtained on three other eyes (R. A. M., R.E.; M. G. B., R.E., L.E.). The measurements on the eyes of M. G. B. showed less tendency to rapid flow rate at high pressures than the eyes of R. A. M. The eyes of M. G. B. also showed a somewhat greater scatter in results than the eye demonstrated in Figure 5.

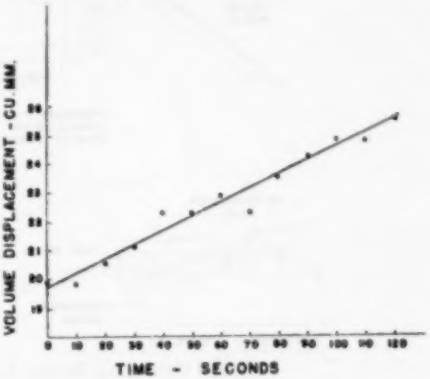

Fig. 1 (Moses and Bruno). A plot of the volumes against time.

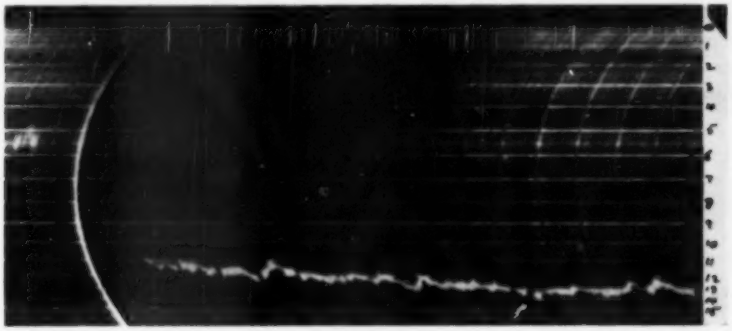

Fig. 2 (Moses and Bruno). Record photographed from electronic tonometer. Experiment No. 271 on the right eye of Subject R. A. M. 5.5-gm. weight, preliminary reading; 10-gm. weight, compression. Crescentic white lines are time markers, 10 seconds apart.

Eyes treated with drugs

A brief survey of the effect of various drugs on the rate of flow was made on the two eyes most carefully studied (R. A. M., L.E.; M. G. B., L.E.). In Figure 6 the general normal limits and the limits for the left eye of Subject R. A. M., under normal conditions are both indicated.

* V. Mueller and Co. very kindly constructed for us an electronic tonometer with a highly damped indicator needle, which, we feel, greatly simplifies visual recording. For photographic recording the undamped indicator is more sensitive.

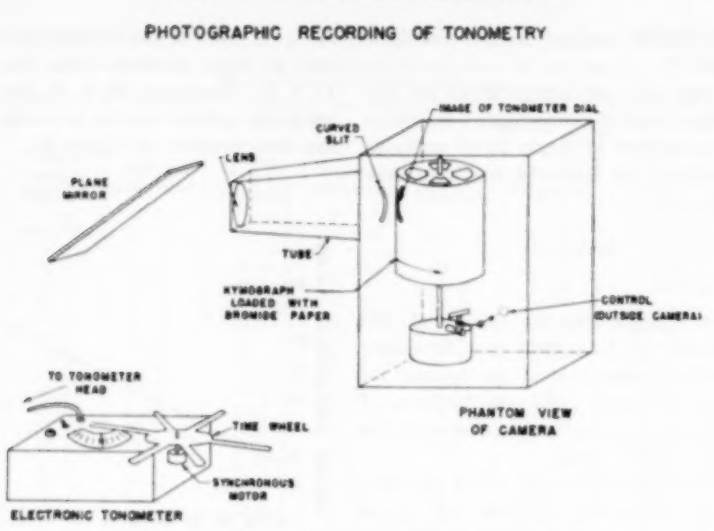

Fig. 3 (Moses and Bruno). A diagram of the apparatus used for photographic recording.

Neosynephrin (10 percent). Three instillations were given five minutes apart, and measurements were made one-half hour and one hour following instillation. The results are within the limits of normal.

Homatropine (2 percent). Three instillations were given five minutes apart and measurements were made 1¼ hours after the third instillation. No deviation of results beyond limits of normal.

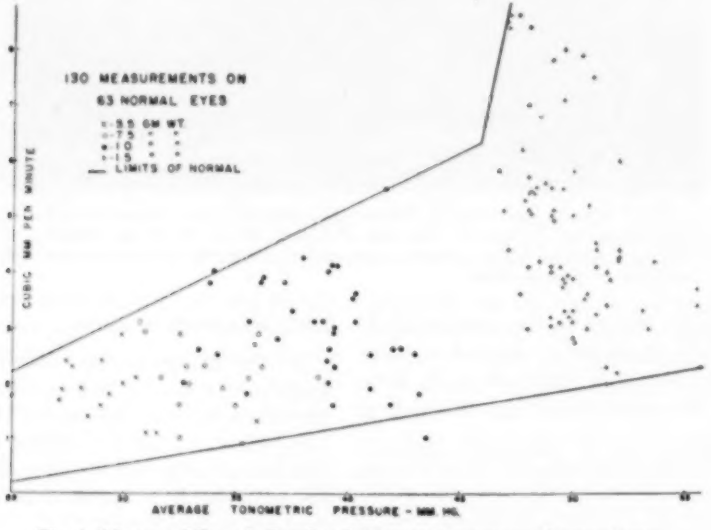

Fig. 4 (Moses and Bruno). Results of 130 measurements on 63 normal eyes.

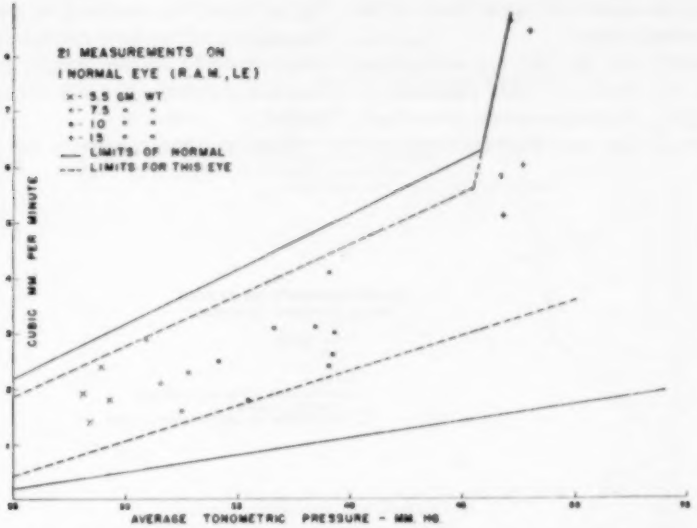

Fig. 5 (Moses and Bruno). Results of 21 measurements on one normal eye.

Eserine (0.25 percent) (one eye: R. A. M., L.E.). Two instillations were given one-half hour apart. Measurements were made at 1¼, 2½, and 4½ hours after the last instillation all on the same day. The results are well within normal limits for this eye.

Pilocarpine (2 percent). Three instillations were given five minutes apart. Measurements were made one-half hour following the third instillation. All four measurements

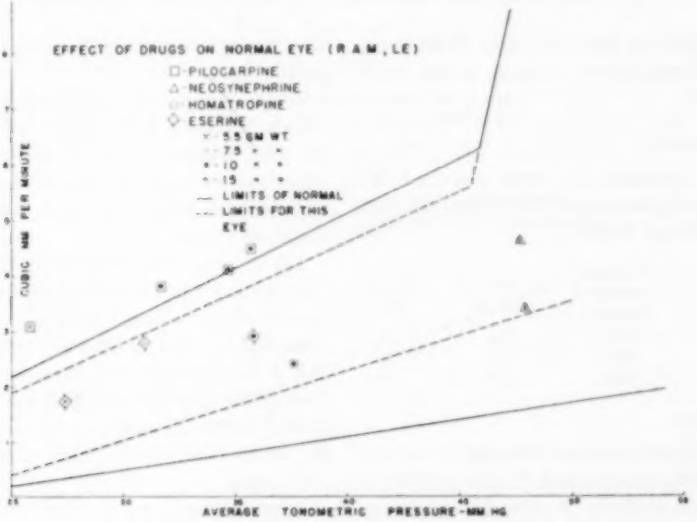

Fig. 6 (Moses and Bruno). Effect of drugs on the rate of flow.

are seen to lie above the upper limit of the general normal range.

The results for the left eye of Subject M. G. B. are similar to those illustrated.

In addition, 14 measurements were made on 14 normal eyes with 2-percent homatropine cycloplegia for refraction. Two measurements were above, 12 were within limits of normal.

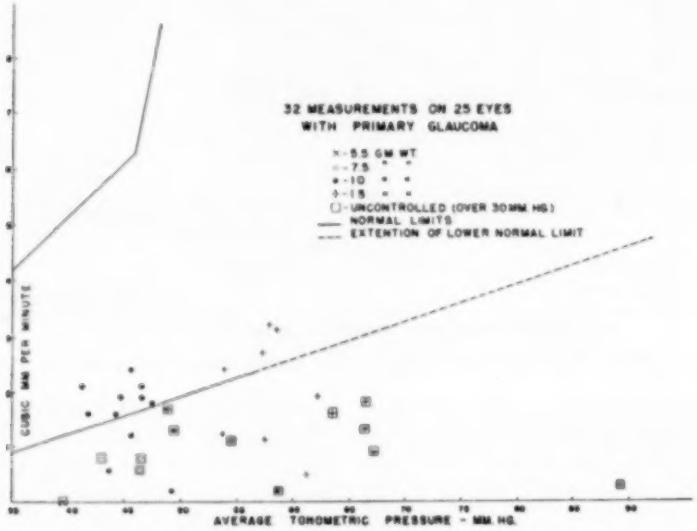

Fig. 7 (Moses and Bruno). Measurements on 25 eyes with primary glaucoma.

High myopia

Three measurements were made on two eyes with high myopia. All three were well within normal limits.

Exp. No.	Average Tonometric Pressure	Cu. mm. per minute	Weight gm.
179	41.9	1.6	10
220	35.9	2.8	10
248	41.6	4.3	15

Glaucoma

A simple and arbitrary standard of control of glaucoma was adopted for the purpose of the present analysis. It was: If a given eye exhibits an intraocular pressure of 30 mm. Hg or lower, as measured by the standard tonometer and the new standard conversion table[3] (usually 5.5-gm. weight reading) *at the time of examination,* it is considered controlled.

Thirty-two measurements were made on 25 unoperated eyes with primary noncongestive glaucoma.

Since gonioscopic observations were not regularly recorded on these cases, and since the total number is too small for elaborate statistical analysis, no effort was made to separate this group into deep- and shallow-angle categories.

All of these eyes were being treated with various drugs or combinations of drugs. The results are given in Figure 7, where it is seen that all rates of flow are relatively low. All of the uncontrolled cases lie below the lower limit of normal or its linear extension. Seven of the controlled cases also lie below the lower limit, while 12 lie within the normal range.

Measurements were made on five eyes with secondary glaucoma (fig. 8). All cases

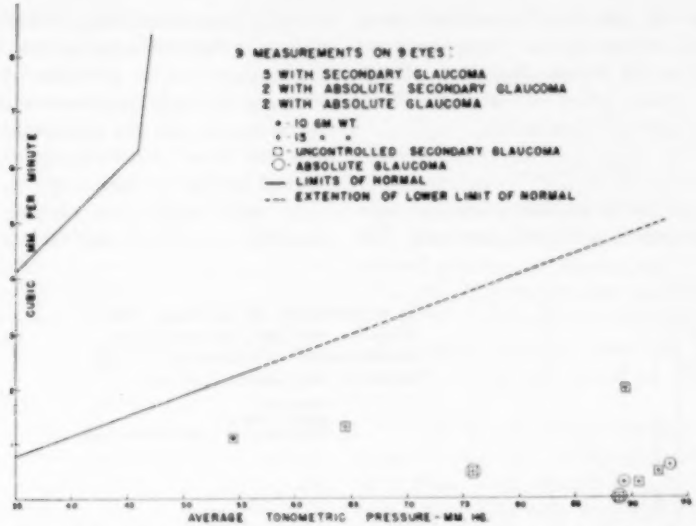

Fig. 8 (Moses and Bruno). Measurements on five eyes with controlled secondary glaucoma, and four eyes with clinically diagnosed absolute glaucoma.

were uncontrolled and all showed very low rates of expression.

Four measurements were made on four eyes diagnosed clinically as "absolute" glaucoma (fig. 8). All showed extremely low rates of filtration.

Twenty-seven measurements were made on 22 eyes with filtering operations for glau-

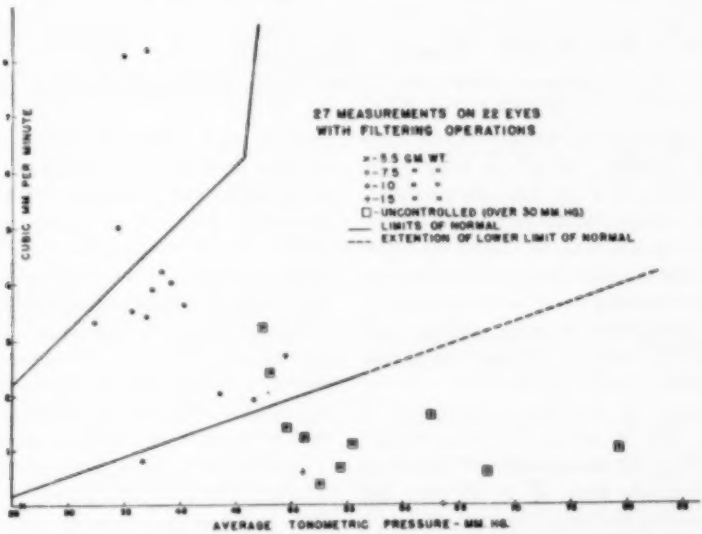

Fig. 9 (Moses and Bruno). Measurements on eyes with filtering operations.

coma (fig. 9). Of the 17 controlled cases, four gave measurements below normal range. Of the 10 uncontrolled cases, all but two gave results below normal limits. Two eyes were too soft to measure.

Discussion

There are several possible sources of error in the procedure we have described. The ordinary tonometric errors have been clearly stated by Priestly Smith.[4] In addition to these we must point out that our use of the tonometer pushes the instrument to its mechanical limits, and it is, therefore, necessary to be certain as to the standard construction and perfect working order of the tonometer. Periodic fluctuations in scale readings may be considerable (fig. 2). We have attempted to use average scale indications.

The range of tonometric pressures is limited to that created by the four standard plunger loads. In the normal eye this range is approximately from 27 to 55 mm. Hg.

In reviewing the results on normal eyes it appears to be fairly probable that there is a direct linear relationship between the rate of loss of fluid from the eye and tonometric pressure, up to the pressure of about 47 mm. Hg. Beyond this pressure some measurements fall into the same linear trend as those at lower pressures. Others show a marked increase in rate.

In experiments upon animals Starling[5] as well as Friedenwald and Pierce,[6] noted a rapid outflow of fluid from the eye at high pressures, and suggested that new paths of exit might be opened. An additional possibility is that the pressure is sufficient to collapse the nutrient arteries to the ciliary body and decrease the production of aqueous, causing an apparent increase in outflow.

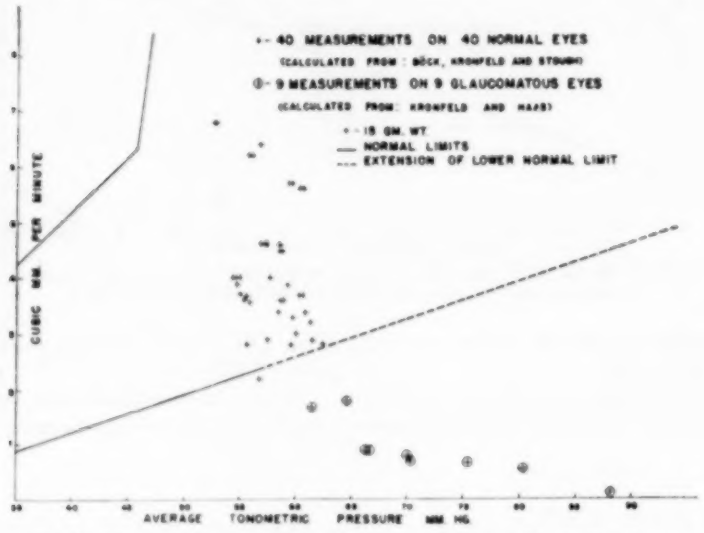

Fig. 10 (Moses and Bruno). Measurements on cases reported in the literature.

Neosynephrin, homatropine, and eserine showed no effect upon the measurements in normal eyes. Pilocarpine, on the other hand, apparently produced an increased rate of outflow of fluid in our experiments.

Most uncontrolled glaucoma cases showed a rate of flow below that of normal eyes, and, in the main, markedly below the normal. Unoperated glaucoma cases controlled

by miotics showed, on the average, a diminished rate of flow but a few of these cases gave results within the normal range. Most cases of glaucoma controlled as the result of filtering operations gave flow rates within the normal range.

Figure 10 represents a group of normal cases (the first 20 cases) reported by Böck, Kronfeld, and Stough,[7] and a group of cases of glaucoma due to peripheral anterior synechias following cataract extraction, reported by Kronfeld and Haas.[8] The figures given by these authors were the intraocular pressures in mm. Hg as determined with a 15-gm. weight and a Schiøtz tonometer. They employed the same experimental technique as we did, leaving the tonometer upon the cornea for two minutes, and reporting the initial and final intraocular pressures. We have worked their figures backward, reducing pressures to scale readings, and have then applied the scale readings to Friedenwald's tables, proceeding as has been described. It is remarkable how well their results agree with ours. There is only a small shift of the normals to the right on the graph.

We have been unable to ascertain whether the fluid which has been expressed from the eye during our experiments is aqueous or blood from the uvea. The procedure has been completely innocuous to all eyes tested.

Summary and Conclusions

1. A method of measuring the outflow of fluid from the intact human eye under elevated pressure, using only the standard Schiøtz tonometer and a timing device is described.

2. This method may be elaborated by photographing the dial of a Mueller electronic tonometer, thus producing a continuous, permanent tonometric record.

3. The rate of outflow of fluid under increased pressure in normal eyes is directly proportional to the pressure in a linear fashion up to a pressure level of about 47 mm. Hg, at which level, in some eyes, a marked increase in rate of outflow of fluid is observed.

4. The effects of neosynephrin, pilocarpine, eserine, and homatropine on the rate of outflow from normal eyes were briefly investigated. The only drug manifesting any effect was pilocarpine, which apparently increased the rate.

5. The rate of outflow from unoperated glaucomatous eyes was, in general, low; most controlled glaucomas gave results in low-normal range; most uncontrolled eyes gave rates distinctly lower than normal.

6. Operated glaucomatous eyes, if controlled, produce results in normal range; if uncontrolled, they produce results below normal range.

The Johns Hopkins Hospital (5).

We wish to thank Dr. Friedenwald for the use of his unpublished data, and for his guidance in this work.

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CRITICAL ANALYSIS OF PRECISION IN TONOMETRY

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The most fundamental problem in the vegetative physiology of the eye, as Duke-Elder points out in one of his recent papers, is the formation and elimination of the intraocular fluid and the control of the ocular tension.

Investigation of the physiochemical questions of this problem has become, due to the latest advances and development of the technical research methods of that branch of science, quite inaccessible to the ophthalmologist in practice and must remain the domain of a pure scientist with a technically well-equipped laboratory.

The control of the ocular tension, a result of the balance of the two vegetative functions of the eye, is equally important to both the scientist and the ophthalmologist.

The scientist will fail to recognize the causes influencing the maintenance of a balance in the formation and elimination of the intraocular fluid, when he cannot depend on sufficient precision in the method of registering the variations of ocular tension.

Without such a precise instrument, the ophthalmologist will fail to detect the early stages of glaucoma or will be unable to appreciate the efficacy of the applied treatment.

The device for this purpose, well known to every ophthalmologist, is the tonometer. What is missing after the many years of its use is a critical attitude toward its precision in registering the variations of ocular tension.

LIMITATIONS OF IMPRESSION TONOMETRY

The impression tonometer most widely used in Europe is that of Schiøtz; in the United States, the Schiøtz and its modifications. The past decades have brought an improvement in the technical aspect and perfection of this instrument but have left in the same state of imperfection its precision in registering the variations of ocular tension.

The basic principle of an impression tonometer is to produce an impression in the center of cornea with a metallic rod of a constant diameter and concavity. The weight of the rod changes from 5.5 to 7.5; 10.0 and 15.0 gm. An increase of ocular tension requires the use of an accordingly greater weight for producing the same depth of impression.

An impression tonometer expresses, in reality, only the depth of the obtained impression in 0.1-mm. units. The height of ocular tension in mm. Hg corresponding to each impression depth is supplied by a table of inversion based on experimental data furnished by Schiøtz a long time ago. A critical study of this table points out the disadvantage of the impression tonometer. Contrary to the basic maxim that every measurement requires the use of a constant invariable unit of measurement, the table of inversion operates with exceedingly variable units. (Chart 1).

The unit of measurement for the impression tonometer changes (1) for each weight of the impression rod used with increasing impression depth (maximal impression produces the smallest obtainable unit of measure, and as the impression depth decreases the unit increases); (2) for each change to a greater weight of the impression rod.

Even with the use of an impression rod of one weight, according to Schiøtz an unadvisable procedure, an invariable unit of measurement of the ocular tension cannot be obtained. The unit of ocular tension for the weight 5.5 gm. is 2 mm. Hg within the impression depths from 0.6 to 1.0 mm.; 3 mm. Hg—from 0.5 to 0.6 mm.; 4 mm. Hg—from 0.3 to 0.5 mm.; 5 mm. Hg—from 0.2 to 0.3 mm.; 6 mm. Hg—from 0.1 to 0.2 mm.; and 7 mm. Hg for the impression depth of 0.1 mm. from the 0 point. The difference between the smallest unit of measurement,

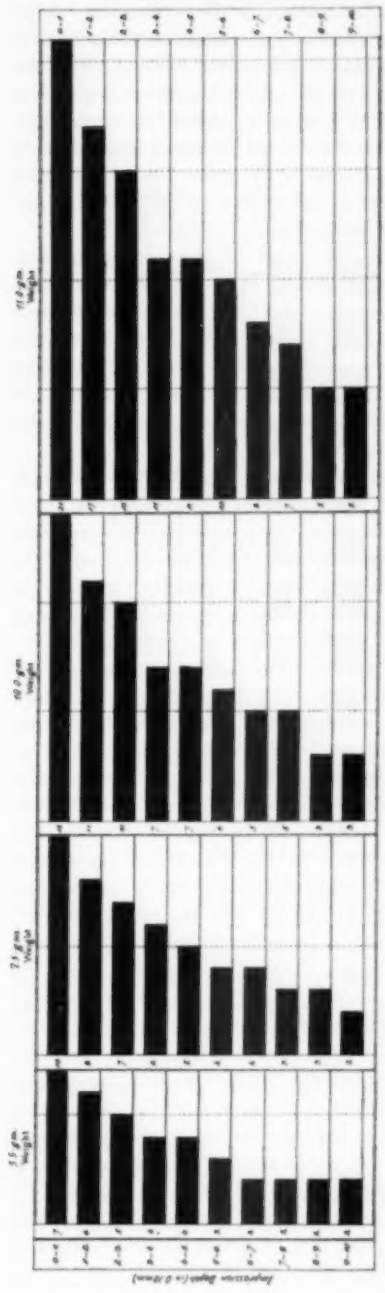

Chart 1 (Apinis). The units of measure of the Schiötz tonometer in mm. Hg.

2 mm. Hg, and the largest of 7 mm. Hg is 5 mm. Hg.

These variations in ocular-tension measurement units increase with the change to the next greater weight of the impression rod.

Inaccuracies in impression tonometer readings are obscured because the ocular tension is expressed in mm. Hg without the used weight of the impression rod being mentioned. For example, an intraocular pressure of 20 mm. Hg can be the result of an application of 5.5-gm. weight, an impression depth of 0.6 mm., the unit of measurement being in that case, 3 mm. Hg. The same tension (20 mm. Hg) can be the result of the application of a 7.5-gm. weight and an impression depth of 0.8 mm., or, as another example: an ocular tension of 40 mm. Hg can be measured with a weight of 7.5 gm., an impression depth of 0.3 mm., a unit of measurement of 7 mm. Hg, as well as with the weight, 10.0 gm., impression depth, 0.5 mm., measurement unit, 7 mm. Hg. A record of the used weight and the depth of the obtained impression should never be omitted, since only these data reveal the precision of each measurement.

It must also be remembered that the readings of the impression tonometer are based on the mathematical average of many different findings. It is possible that the ocular tension deduced on the basis of the impression depth coincides with the real ocular tension. The possibility (proved experimentally) remains, however, that the tonometric readings are lower than the actual ocular tension. This could be overlooked if the unit of measurement was very small, but that cannot be said of the impression tonometer with an average unit of measurement of 5 mm. Hg.

These disadvantages, characteristic of every impression tonometer, inspired me to a manometric and clinical investigation of the use of the applanation principle in tonometry.

Limitations of applanation tonometry

The use of the applanation principle in tonometry permits two different procedures. The amount of ocular tension can be calculated (1) by the size of the applanation diameter under a constant weight or (2) by the weight necessary to obtain an applanation diameter of a constant invariable size.

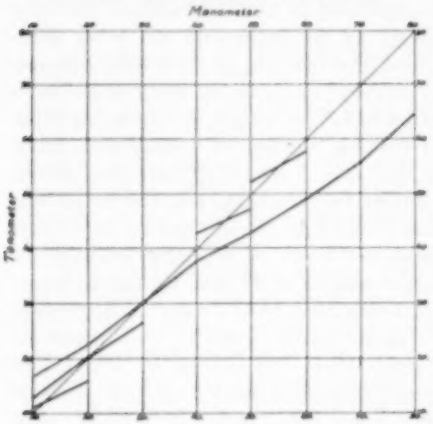

Chart 2 (Apinis). The relationship of tonometric readings and manometric tension. The weights used (reading from bottom to top) 5 gm., 7.5 gm., 10 gm., 25 gm., and 30 gm.

While all the readings in the use of the impression principle are based on the mathematical average of experimentally found data, the applanation principle gives results based on pure mathematical calculations. Imbert, Fick, Maklakow, and others are convinced that by the use of the applanation principle, mathematical calculations can express the real ocular tension, and that the influence of such factors as the elasticity of cornea and sclera are practically negligible.

Determination of ocular tension by size of applanation diameter

When the size of the applanation diameter is used to determine ocular tension, the tonometer of Maklakow is used. Manometric investigations on cadaver eyes in situ prove a very interesting fact—under certain conditions, the mathematically calculated ocular tension coincides in reality with the manometric controlled ocular tension. For the 10.0 gm. weight of the Maklakow tonometer, this occurs when the size of the applanation diameter reaches the limit of 5.6 mm. In that case, the tonometric ocular tension coincides with the actual tension of 30 mm. Hg controlled by manometer (Chart 2).

From this point of coincidence upward, the difference between the tonometric and manometric ocular tension increases progressively, the tonometric readings being less than the actual ocular tension. Downward from this point, the tonometric readings are higher than the manometric-controlled ocular tension.

Such an intersection of the curve of tonometric readings with the manometric curve suggests that it might be possible to obtain a coincidence of the tonometric with the manometric-controlled ocular tension at every level, using a gradually increasing weight of the tonometer (Kalfa, Apin).

Manometric investigations (Apin) proved that such a coincidence can be obtained. Some examples from those studies confirm this. Chart 2 reveals the evidence that for every weight of the tonometer such a point of coincidence with the manometric controlled ocular tension can be reached. The intersections of the tonometric curve with that of manometer are given for several weights (Chart 2). For the weight 5.0 gm., the point of coincidence lies at 12 mm. Hg; for 7.5 gm. at 20 mm. Hg; for 10.0 gm., at 30 mm. Hg; for 25.0 gm., at 46 mm. Hg; and for 30.0 gm., at 56 mm. Hg.

Observations made during these researches emphasized the necessity of using an increasing weight of the tonometer for an increase in ocular tension. The size of the applanation diameter should not be less than 6.0 mm. at low ocular tension and not exceed 7.0 mm. at high ocular tension. Within these limits, the size of the applanation diameter should be gradually increased in conformity

with increasing ocular tension. In practice it is, therefore, unnecessary to use a table for inversion of the tonometric readings in mm. Hg based on experimental average findings; that can be done using data furnished by mathematical calculations.

The inversion of the size of the applanation diameter into the corresponding mm. Hg of ocular tension requires an inversion table whose data are mathematically calculated. The measure units of ocular tension for every size of the applanation diameter and

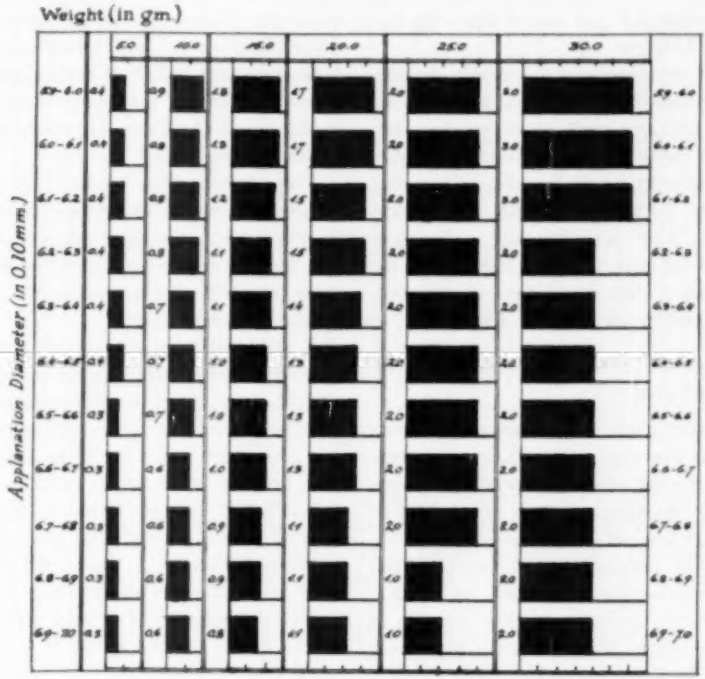

Chart 3 (Apinis). The units of measure of the applanation tonometer with determination of tension by the size of the applanation diameter (in mm.).

The precision of this method for the determination of ocular tension, as compared with that of impression tonometry, is considerable. The same measure unit of 0.1 mm. is used to determine the size of the applanation diameter. All attention during the tonometry can be fixed on the correct application of the tonometer. The applanation diameter obtained is always printed on paper as soon as the instrument is taken off the eye. The printed diameter can be measured later at ease with every devise necessary to increase accuracy.

every used weight are shown in Chart 3. It is true that this method has the same disadvantages of variable measure units for (1) every change in the size of applanation diameter for each weight and (2) every change to another weight for each size of the applanation diameter that impression tonometry has.

The actual value of this method for the determination of ocular tension lies in a considerably higher precision. The variations of the measure units with a change of the size of applanation diameter are minimal and can

be ignored. The difference between the minimal and maximal measure units for the weight 5.0 gm. is only 0.1 mm. Hg; for 10.0 gm., 0.3 mm. Hg; for 15.0 gm., 0.5 mm. Hg; for 20.0 gm., 0.6 mm. Hg; for 25.0 gm. and 30.0 gm., 1.0 mm. Hg. The same differences for the impression tonometry are 2 mm. Hg for the weight 5.5 gm. and 3 mm. Hg for the weight 15.0 gm.

Units of measurement for ocular tension in both methods, impression and applanation, drawn on the same scale, allow an easy comparison of those different procedures. Table 1 shows the units for the impression tonometer; Chart 3, those for the applanation tonometer. The precision of applanation tonometry exceeds that of impression tonometry many times and for scientific research should be the method of choice.

Obtaining an applanation diameter of constant size

The assumption that more exact tonometric data are reached by using a progressively increasing weight to produce an impression or an applanation is recognized in the construction of the Fick-Livschitz tonometer. The standard size (6.8 mm.) of the applanation diameter is based on mathematical calculations that make it possible to double the applied weight in order to express the ocular tension in mm. Hg. For example: a pressure on the eye with a weight of 10.0 gm. produces the applanation diameter of 6.8 mm. and the ocular tension in that case is $2 \times 10 = 20$ mm. Hg; the same applanation diameter with a pressure of 15.0 gm. gives an ocular tension of $2 \times 15 = 30$ mm. Hg, and so on.

The scale graduation of the Fick-Livschitz tonometer records the increase of pressure on the eye in steps of a 1.0-gm. weight for each grade. The unit of measurement—2 mm. Hg—is, therefore, always constant and invariable.

The application of this tonometer is very simple and can be done while the patient is seated. Its disadvantage is that the operator's attention must be divided between consideration of the size of the applanation diameter and the reading of the applied weight.

The size of the applanation diameter, 6.8 mm., must be judged with the naked eye. The possibility cannot be denied that a mistake can be made in the appreciation of the actual size of the applanation diameter which could be 6.7 or 6.9 mm. instead of 6.8 mm. Such a mistake would of course, give an incorrect reading of the ocular tension which would actually be 2 mm. Hg lower or higher, as the case might be.

These peculiarities of the Fick-Livschitz tonometer prohibit its use in precise scientific researches, although it will remain in general use for recording the ocular tension in cases in which an error of 2 mm. Hg more or less is not important.

A very slight change in procedure would, however, permit its use in scientific researches: the size of the applanation diameter actually reached should be printed on paper—a procedure which simplifies this tonometer's use and increases its precision because the attention can be fixed on reading the applied weight. The size of the printed applanation diameter is measured afterward with ease and every desired accuracy.

This procedure also permits determination of the ocular tension either by (1) the applied weight or (2) the size of applanation diameter. The precision of the measurement by the size of applanation diameter is greater and to be preferred. The measure unit is under 1 mm. Hg, if the used weight does not exceed 10.0 gm.; under 2 mm. Hg, if the weight does not exceed 20.0 gm., and 2 mm. Hg for the weights 25.0 gm. and 30.0 gm.

The construction of the Fick-Livschitz tonometer permits an increase of the weight in 1.0 gm. steps. However, in determining ocular tension by the size of applanation diameter, the applied weights can be restricted to 5.0-gm. steps (5, 10, 15, 20, 25, and 30 gm. weights).

Chart 2, with its experimental data, shows that the point of coincidence between tono-

TABLE 1

THE VARIATIONS OF OCULAR TENSION IN A CASE OF GLAUCOMA*

Date	Right Eye							Left Eye						
	Applanation Tonometer				Impression Tonometer			Applanation Tonometer				Impression Tonometer		
	Weight (in gm.)	Applanation Diameter (in mm.)	Tension (in mm. Hg)	Measure Unit (in mm.)	Weight (in gm.)	Impression Depth (in mm.)	Measure Unit (in mm. Hg)	Weight (in gm.)	Applanation Diameter (in mm.)	Tension (in mm. Hg)	Measure Unit (in mm.)	Weight (in gm.)	Impression Depth (in mm.)	Measure Unit (in mm. Hg)
7/16/47	20	6.8	39	1.1	10.0	5	7	20	6.8	39	1.1	10.0	5	7
7/22/47	15	6.8	31	0.9	7.5	5	5	20	6.7	40	1.1	10.0	5	7
7/25/47	15	6.9	30	0.9	7.5	5	5	15	6.4	35	1.1	10.0	6	4
9/ 4/47	20	6.6	41	1.3	10.0	5	7	20	6.9	38	1.1	10.0	5	7
9/11/47	20	6.8	39	1.1	10.0	5	7	20	6.9	38	1.1	10.0	5	7
9/12/47	20	6.9	38	1.1	10.0	5	7	15	6.4	36	1.1	10.0	6	4
9/13/47	20	6.7	40	1.1	10.0	5	7	15	6.5	34	1.0	10.0	6	4
9/14/47	20	6.8	39	1.1	10.0	5	7	15	6.5	34	1.0	10.0	6	4
9/16/47	10	6.8	20	0.6	7.5	8	3	20	6.8	39	1.1	10.0	5	7
9/17/47	15	6.8	31	0.9	7.5	5	5	20	6.8	39	1.1	10.0	5	7
9/18/47	10	6.4	23	0.7	7.5	7	4	20	6.9	38	1.1	10.0	5	7
9/19/47	10	6.4	23	0.7	7.5	7	4							
9/20/47	10	6.8	20	0.7	7.5	8	3	10	7.1	19	0.6	7.5	8	3
9/21/47	10	6.8	20	0.6	7.5	8	3	10	6.8	20	0.6	7.5	8	3
9/22/47	10	7.0	19	0.6	5.5	6	3	10	6.4	23	0.7	5.5	5	4
9/23/47	10	7.1	19	0.6	5.5	6	3	10	6.2	25	0.8	5.5	5	4
9/24/47	5	6.3	12	0.4	5.5	10	2	10	6.5	22	0.7	5.5	5	4
9/25/47	5	6.2	12	0.4	5.5	10	2	5	6.2	12	0.4	5.5	10	2
9/28/47	5	6.4	11	0.4	5.5	10	2	5	6.1	13	0.4	5.5	10	2
9/30/47	5	6.3	12	0.4	5.5	10	2	5	6.1	13	0.4	5.5	10	2
10/ 9/47	5	6.3	12	0.4	5.5	10	2	5	6.3	12	0.4	5.5	10	2
10/13/47	5	6.3	12	0.4	5.5	10	2	5	6.4	11	0.4	5.5	10	2
10/16/47	5	6.4	11	0.4	5.5	10	2	5	6.3	12	0.4	5.5	10	2
10/27/47	5	6.3	12	0.4	5.5	10	2	5	6.3	12	0.4	5.5	10	2
10/30/47	5	6.2	12	0.4	5.5	10	2	5	6.3	12	0.4	5.5	10	2

* The data for applanation are actual, for impression hypothetic.

metric and manometrically controlled ocular tension shows a spread of only minus 2.0 mm. Hg, on increase of tension and of not more than plus 2.3 mm. Hg on decrease of tension. In practice, the difference will really never reach that amount, for, when the alterations in ocular tension (increase or decrease) exceed 5 mm. Hg, the next smaller or larger weight can be used. For very delicate research the applied weight can always be increased in 1.0 gm. steps.

The precision of the procedure just mentioned is shown in Table 1. The Fick-Livschitz tonometer was used to register the changes in ocular tension in a case of glaucoma under conservative treatment with drugs after cyclodialysis (R.E., September 14; L.E., September 18, 1947). The procedure of printing the applanation diameter on paper was followed, using the 5, 10, 15, and 20 gm. weights.

Table 1 gives all essential data: (1) The applied weight, (2) the size of the obtained applanation diameter, (3) ocular tension deduced from the size of applanation diameter, and (4) the unit for each measurement. The

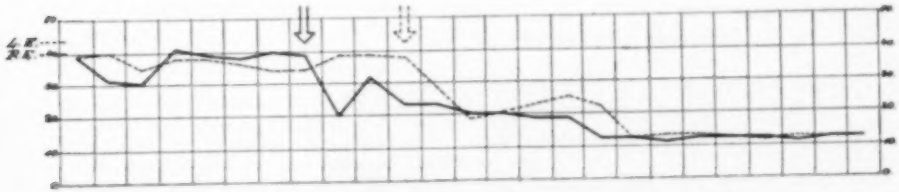

Chart 4 (Apinis). A curve of the variations in ocular tension in a case of glaucoma as constructed from the data in Table 1.

maximum measure unit does not exceed 1.3 mm. Hg in the right eye, and 1.1 mm. Hg in the left eye; the minimum measure unit is 0.4 mm. Hg.

For comparison, hypothetical data for an impression tonometer have been added to Table 1. The maximum measure unit for the

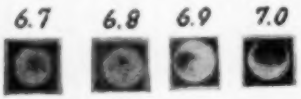

Fig. 1 (Apinis). Examples of printed applanation diameters in their original sizes (in mm.).

impression tonometer is 7 mm. Hg; the minimum 2 mm. Hg. Under such circumstances it can hardly be expected that, in practice, the curve of the impression tonometer will coincide with that of applanation tonometer, because the maximum measure unit of the applanation tonometer (1.3 mm. Hg) is less than the minimum measure unit of the impression tonometer (2 mm. Hg). When the impression tonometer is used, subtle changes of ocular tension will remain undetected.

The graphic expression of the variations of ocular tension in a case of glaucoma is shown in Chart 4. Examples of printed applanation diameters in their original sizes are shown in Figure 1.

Summary

Recent improvements in the Schiøtz impression tonometer and its modifications have increased its technical perfection but left its precision at the same state of imperfection.

The use of applanation tonometry should be preferred in scientific researches because of its greater precision and because printing the size of the applanation diameter permits exact measuring.

At present the Fick-Livschitz tonometer is best for use in applanation tonometry: (1) In practice because of ease of application with the patient in a seated position, and (2) in scientific researches because (a) the printing of the applanation diameter increases its precision and (b) the appliance of gradually increased weight in conformity with increased ocular tension gives more reliable readings.

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THE NUTRITIONAL SUPPLY OF CORNEAL REGIONS IN EXPERIMENTAL ANIMALS*

I. The supply of some inorganic ions

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(With the technical assistance of Mildred Orchen, B.A., and Doris Goodman, B.A.)
Cleveland, Ohio

The problem of the access of nutrients to the avascular cornea has been periodically reinvestigated since the earliest days of eye research. The early work of Gruber[1] on the coloration of corneal rust spots by injected ferrocyanide gave the first clue to the role of the limbal plexus in corneal nutrition. Other papers of this period are reviewed by Leber in his monograph.[2] Work in the 1920s was led by Fischer,[3] who described the differential permeabilities of the epithelial and endothelial surfaces. Most recently the work of Cogan and Kinsey[4] has presented a new outlook on the water balance of the cornea and the importance of fat solubility in massive penetration of the corneal epithelium.

As long as the classic view[2] prevailed; namely, that the metabolic activity of the cornea was negligible, the quantitation of the nutritional supply was a matter of academic interest only. However, the recent work of the Wilmer group[5] has demonstrated a modest but measurable oxidative and glycolytic activity for the cornea with individual anatomic and biochemical characteristics hitherto unsuspected.

Moreover, the corneal lesions of certain nutritional deficiencies[6] and their similarity to certain idiopathic clinical diseases[7] has emphasized the possibility that imbalance between nutritional supply and metabolic demand may be at the basis of some diseases of the cornea.

Scope of present experiments

With these considerations, we have begun a study of the quantitative role played by each of the three potential sources of nutritional supply—the limbal circulation, the tears, and the aqueous humor, using type substances for the purpose. Because of the ease of accurate analysis of minute quantities, which it affords, tracer technique with radioactive isotopes has been employed where possible.

In order to orient our studies and to provide a point of departure for future work, some of the more easily available inorganic ions have been investigated first. Results to be reported in this preliminary study have been obtained with phosphate using P^{32}, with sodium using Na^{24}, with iodide using I^{131}, and with Cesium using Cs^{134}.†

We have made studies on the rate of disappearance of these ions from blood and the rate of their appearance in the cornea and in tears after intravenous injection. We have studied their entrance into the cornea after injection into the anterior chamber, or subconjunctivally, and after application to the anterior surface of the eye in situ. In one set of experiments we compared the rate of entry into an eye where the limbal plexus had been damaged (by chemical cauterization) to the rate of entry into a normal eye. Rabbits were used in all the tracer experiments described.

Experimental intravenous administration of labeled compounds

All rabbits were under barbiturate anes-

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† All inorganic ions used in this study were obtained through the U. S. Atomic Energy Commission, Oak Ridge, Tennessee.

thesia. In addition it was usually necessary to use a 0.5-percent isotonic solution of pontocaine for conjunctival anesthesia at the time of enucleation.

The compounds used were given in 5 cc. of aqueous solution. The solution usually contained a small quantity of fluorescein sodium to facilitate possible radioactive decontamination. The amount of radioactivity needed to make measurement of corneal regions feasible was in the neighborhood of 100 microcuries; the exact absolute amount is unimportant because all unknowns were compared to standards measured at the same sitting. There is no evidence that this quantity of radioactivity given to a 2.5- to 3.5-Kg. rabbit has any effect on the permeability characteristics of the animal's cells. The injected solution contained, in addition, the following amounts of nonradioactive salts:

TABLE 1

AREAS OF CORNEAL RINGS

Cork Borer	Radius (cm.)	Area of ring (cm.²)
7	0.665	(7–6) = 0.30
6	0.587	(6–4) = 0.49
4	0.435	(4–2) = 0.366
2	0.269	(2) = 0.228

a. Sodium: 25 mg. Na. This represents some 6.5 percent of the normal serum sodium content and is negligible in comparison with it. Thus one is actually measuring the behavior of serum sodium.

b. Phosphate: 1.6 mg. P. This represents approximately 21 percent of the circulating inorganic phosphate in a 2.5 Kg. rabbit. Here, too, we are probably measuring the behavior of the serum inorganic phosphate.

c. Iodide: 250 μg. I. There is probably no more than 1 to 2 mg. of inorganic iodine circulating in the normal 2.5 Kg. rabbit. Hence the introduction of this quantity of iodide results in an unusually high blood concentration.

d. Cesium: 7.5 mg. Cs. Since cesium occurs in the body in only the minutest traces, any measurable amount of carrier would result in unusually high tissue concentrations. However, since cesium is an alkali metal and since the above amount is small in comparison with that of the sodium and potassium present, we were interested in studying the behavior of this ion.

TECHNIQUE

At zero time the tracer solution was injected into the marginal ear vein of the rabbit. When the strength of the gamma emission so indicated, the syringe was shielded with lead. At predetermined intervals, 3-cc. samples of blood were withdrawn by cardiac puncture.

At appropriate times the eyes were dissected out and, after a momentary rinse in a stream of physiologic saline from a wash bottle, they were frozen instantaneously in a bath of hexane immersed in a dry ice—"carbitol" mixture. This insured immediate cessation of any further diffusion processes. The frozen eyes were removed from the bath in a cold room at −10°C. and all dissection was completed while the eyes were still frozen.

Corneas were cut out with a No.-7 cork borer (diameter 13.3 mm.), carefully freed of aqueous, and flattened on a blotter. To avoid the possibility that the outer edge of the cut cornea might be contaminated by the contents of limbal or choroidal circulation deposited by the cork borer, a No.-6 cork borer was used to cut a slightly smaller concentric disc. This disc was then cut into two concentric circles and a center circular plug by the use of a No.-4 and No.-2 cork borer. The areas of these pieces are given in Table 1.

Each piece was weighed to 0.1 mg. on a torsion balance and was placed in an individual 2-oz. ointment tin for digestion and isotope determination. Samples of aqueous, lens, and vitreous were taken similarly.

Each tissue sample was then allowed to

thaw, 1 cc. of 5-percent NaOH was added, and the tissue was allowed to disintegrate in the heat of an infrared lamp, water being added from time to time to replace that lost by evaporation. With the iodide samples a small amount of carrier iodide and sodium sulfite were added to the base to insure against loss of iodine by volatilization.

After disintegration was complete, a matter of 10 minutes or less for corneas, 1 cc. of a dilute solution of detergent* was added to allow even distribution of the digest over the bottom of the tin and the solution was allowed to evaporate to dryness. Radioactivity was then determined with a large-windowed Geiger-Muller tube† and a suitable scaling circuit.‡

Because of the large (29 cm.²) area of the ointment tin and the large-windowed tube, corrections for self-absorption of corneal samples were not ordinarily required. At the same time the tissue samples were prepared, aliquots of the serum samples and of a dilution of the original injection solution were prepared in tins in a similar manner and counted at the same time as the corneas.

In one set of experiments it was desired to close off the limbal plexus, if possible, in order to evaluate the eye after this source of supply had been eliminated. Because of the proximity of the limbus to the ciliary apparatus in the rabbit, our first attempts to accomplish this end by limbal diathermy resulted in very low activity in both aqueous and cornea. Presumably the limbal vessels plus the ciliary apparatus had been destroyed. Section of the rectus muscles plus the conjunctiva had little effect on the corneal or aqueous values. If anything, it increased them, perhaps because of the induced hyperemia. The procedure finally employed consisted in sectioning the conjunctiva, severing the recti at their insertions, and then applying a silver-nitrate stick to the limbal region.

When it was desired to collect tear samples, the flow of tears was induced by the intravenous injection of 0.5 cc. of solution containing 3 mg. of pilocarpine nitrate. Two or three minutes after the injection, tear samples of 25 to 100 cubic millimeters could be drawn into micropipettes from the conjunctival sac. These tears were the characteristically "milky" ones described by previous investigators.

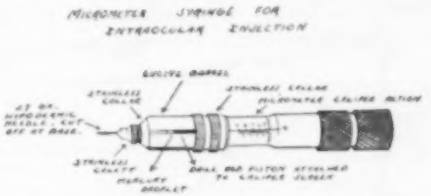

Fig. 1 (Potts and Johnson). Special micrometer syringe for subconjunctival and intraocular administration.

The subconjunctival and intraocular administration was accomplished by means of a special micrometer syringe¶ illustrated in Figure 1. The drill-rod piston of the syringe is activated by the screw of a micrometer caliper which is preserved intact with its graduated scale. The accurately drilled lucite barrel was fitted at its end with a stainless steel collet, designed to hold a 5/8" by 27-gauge hypodermic needle which had been cut off in a lathe at the junction of the conical and square portions of the hub. These needles were cut off for us by the shop in lots of several dozen and afforded an inexpensive and replaceable stock. The seal between the needle and the bore was accomplished with a small replaceable plastic gasket.

The syringe was ordinarily operated with a droplet of mercury ahead of the piston to prevent possible contamination of the screw. Dimensions were so arranged on our model

* A one-percent solution of a number of commercially available detergents serves this purpose.
† Cyclotron Specialties, Moraga, California.
‡ Tracerlab Autoscaler.

¶ Made for us by Northern Tool Company, Cleveland, Ohio.

that two complete turns of the screw, that is, 50 thousandths of an inch travel of the piston delivered 0.86 cubic mm. of solution with a reproducibility of approximately 7 percent. Larger volumes could be delivered with correspondingly greater accuracy. The total content of the syringe is approximately 15 cubic millimeters. For injection into the anterior chamber, the needle was either left

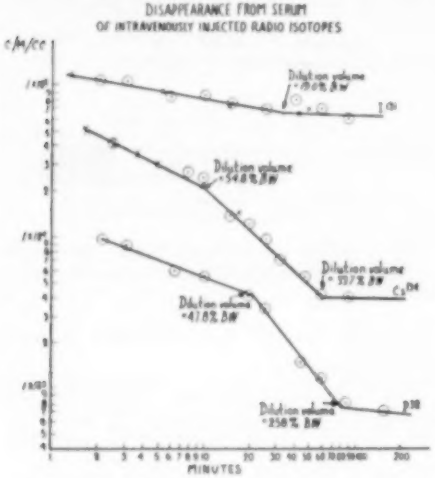

Fig. 2 (Potts and Johnson). Graph for iodide, cesium, and phosphate.

in situ for the duration of the experiment or cut off as described by Kinsey and others.[8]

For topical application a glass tube 5 mm. in diameter with a flanged lower edge for contact with the cornea was used. The radioactive solution was imbibed on a small piece of absorbent cotton in the tube, the tube put in place on the cornea, and the cotton gently pushed in contact with the cornea by means of an attached piece of wire. For the relatively short times of the experiments, the tube was held in place by hand. At the end of the experiment, the eye was washed copiously with saline and dissected while frozen. The area of application was cut out of the cornea by an appropriate sized cork borer. The rest of the cornea contained negligible amounts of activity.

Results

Blood levels

The disappearance from the blood of intravenously injected diffusible substances has been discussed extensively by Hevesy.[9] Theoretical treatment has been meager, all based on the assumption that the rate of loss from the blood stream is proportional to the

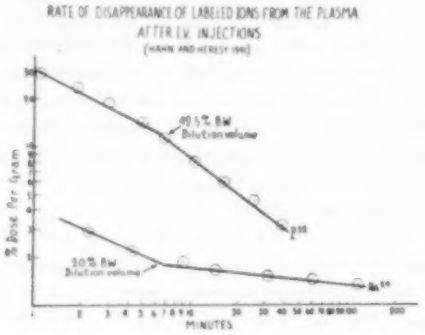

Fig. 3 (Potts and Johnson). Values of phosphate and sodium obtained by Hahn and Hevesy.[12]

concentration of the substance in the blood (Palm[10, 11]).

On this assumption a simple exponential relationship between blood level and time should obtain and a plot of log blood level vs. time should give a straight line. When our figures for blood levels were so plotted, a straight line did not result. However, when log blood level is plotted against log time the result is a straight line with 1 or 2 changes of slope.

Such a graph for iodide, cesium, and phosphate is shown in Figure 2. Where two sets of symbols are indicated, the curve is a composite of two experiments with the values of one experiment corrected by a constant factor. To show that there is nothing unique about our experiments the values for phosphate and sodium obtained by Hahn and Hevesy[12] were similarly plotted with similar results (fig. 3).

It is evident from these curves that two different types of behavior are being manifested. In the case of iodide and sodium the

rate of loss from the blood stream is relatively low. The dilution volume, a term introduced by Hevesy[12] to indicate the weight in grams in which the original activity must be diluted to give the concentration found, can be expressed as percent body weight of the animal.

For iodide and sodium the dilution volumes run some 20 percent of body weight at the point of flexion and, after this point, the slope is less than, not greater, than it was before. In the case of the cesium and the phosphate, dilution volumes are already 50 percent of the body weight at the first flexion and the slope is greater than before. With both of these substances a second flex occurs at 327 percent and 258 percent of body weight, respectively, and from here the curve becomes almost flat.

Whatever may be the physiologic significance of these manifestations, as discussed below, the practical consequence is that over long-time ranges blood values may be accurately interpolated and extrapolated using only two blood determinations, and this was made use of in the subsequent work.

Levels of isotope in the cornea

It is reasonable to suppose that the driving force for the entry of an ion into tissue is the concentration gradient between blood and tissue and, in the early portion of the experiment, this is practically equivalent to the blood level. Theoretically, then, the level of ion in the corneal ring nearest the blood at any given time should be proportional to the product of time and mean blood level to that time. Otherwise expressed, this is the area under the concentration-time curve for blood.

Since it is impractical to attempt such a calculation for each eye investigated and since the shape of the blood time curve is clearly known, it might be expected that if the corneal outer-ring figures were related to the blood level at some fixed time, the resultant ratios would generate a curve with time that fell as the blood level rose and that might be amenable to theoretical treatment.

TABLE 2

Concentration of Na^{24} in corneal rings after intravenous injection expressed as percent serum level at five minutes

Time (min.)	Cornea Outer Ring	Cornea Middle Ring	Cornea Center Plug	Aqueous
3.2	2.5	0	0	2.3
4.4	4.0	1.4	2.3	4.3
6.5	5.1	2.4	1.9	4.7
9.9	9.9	7.2	3.1	11.7

We arbitrarily chose the five-minute blood level as our reference point and the values for isotope content of the corneal rings and the aqueous humor of normal eyes are presented in Tables 2 through 5. The plot of the values for the outer rings against time on logarithmic coördinates are presented in Figures 4 to 7, respectively. To prevent confusion caused by unavoidable scatter of the data the values for the other rings and the aqueous have not been shown graphically. However these values have been recalculated as percent of outer ring content and their means with standard errors are given in Table 6.

From consideration of these tables and figures a number of conclusions are inescapable. There is a rise in corneal content of labeled ion which is rapid at first and then reaches a nearly constant plateau as 20 to 30 minutes are passed. In the case of sodium, the plateau had not yet been reached at the longest time of 10 minutes; in the

TABLE 3

LABELED IODIDE CONTENT OF CORNEAL RINGS AND AQUEOUS HUMOR EXPRESSED AS PERCENT SERUM LEVEL AT FIVE MINUTES

Time (min.)	Cornea Outer Ring	Cornea Middle Ring	Cornea Center Ring	Aqueous
3.0	2.5	0	0	1.3
3.6	4.3	1.4	0.3	3.7
4.0	12.9	3.0	2.2	4.9
6.0	10.5	2.9	—	5.4
6.0	15.9	4.6	8.1	6.1
7.0	17.9	10.7	6.2	14.9
7.0	22.0	12.3	13.7	15.2
8.3	21.3	9.0	5.2	12.1
10.0	21.4	18.3	18.8	15.9
11.6	35.7	38.6	22.0	20.6
12.5	39.6	37.6	33.4	17.3
13.5	26.0	14.2	11.5	13.4
19.2	17.5	10.6	9.5	10.4
24.0	70.7	61.9	60.1	43.7
48.0	33.8	20.9	19.4	21.0
60.0	29.2	20.4	21.2	17.5
62.0	43.1	44.0	54.6	27.1
63.0	35.3	30.2	24.8	25.3
96.0	50.5	48.8	46.6	30.4

TABLE 4

LABELED CESIUM CONTENT OF CORNEAL RINGS AND AQUEOUS HUMOR EXPRESSED AS PERCENT SERUM LEVEL AT FIVE MINUTES

Time (min.)	Cornea Outer Ring	Cornea Middle Ring	Cornea Center Ring	Aqueous
5.0	8.9	4.2	2.8	7.7
6.0	8.7	6.0	5.4	14.5
7.0	12.4	14.5	6.1	4.7
10.5	22.2	18.9	15.8	18.5
20.2	19.9	22.4	15.2	15.3
21.0	19.0	10.0	8.7	7.8
22.4	15.7	12.9	18.6	14.8
30.8	25.0	21.0	17.1	38.5
60.0	22.9	21.2	19.8	13.0
120.0	26.1	23.2	25.0	11.4

TABLE 5

LABELED PHOSPHATE CONTENT OF CORNEAL RINGS AND AQUEOUS HUMOR EXPRESSED AS PERCENT SERUM LEVEL AT FIVE MINUTES

Time (min.)	Cornea Outer Ring	Cornea Middle Ring	Cornea Center Ring	Aqueous
6.0	1.8	0.55	0.64	2.6
11.0	9.5	0.59	0.37	4.1
15.0	9.3	2.6	1.2	7.3
15.0	8.8	3.3	1.7	10.7
21.0	9.2	2.7	2.3	5.2
22.0	13.1	4.8	3.7	9.0
22.0	9.6	2.9	2.2	6.5
23.0	9.9	5.2	4.1	10.5
25.0	9.0	7.5	5.4	14.1
25.0	18.5	10.2	4.2	6.4
29.0	20.0	4.4	3.2	6.8
76.0	16.8	13.3	12.1	15.0
127.0	18.3	18.0	12.9	12.2

case of the phosphate, most of the values are already on the plateau. The significance of the actual plateau values will be discussed later.

The difference between the ion content of the outer ring and that of the rest of the cornea is statistically significant for each ion. The area next the limbal plexus has the highest ion content for all four isotopes. This has been confirmed by autoradiographs. The mean differences between the middle ring and the center plug are relatively small and, although in each case the mean for the middle ring is the higher, the differences are not statistically significant for any of the ions. Similarly, the mean for the aqueous humor falls above that for the middle ring in all but the iodide eyes.

The large scatter of the data makes any definite conclusions on the significance of

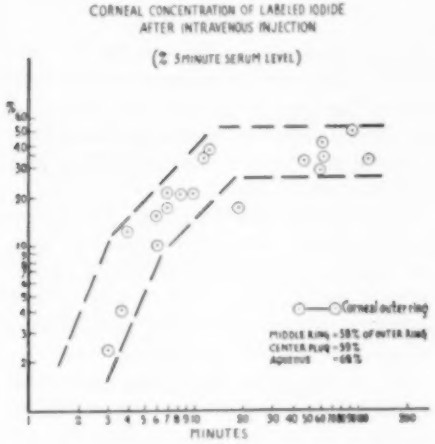

Fig. 4 (Potts and Johnson). The values of the outer rings plotted against time on logarithmic coordinates.

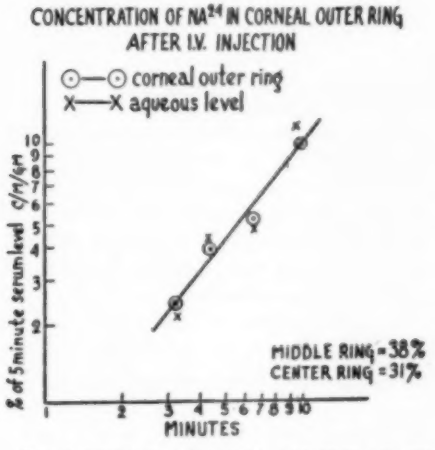

Fig. 5 (Potts and Johnson). The values of the outer rings plotted against time on logarithmic coordinates.

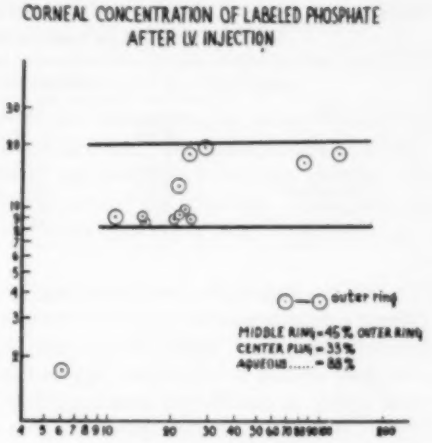

Fig. 6 (Potts and Johnson). The values of the outer rings plotted against time on logarithmic coordinates.

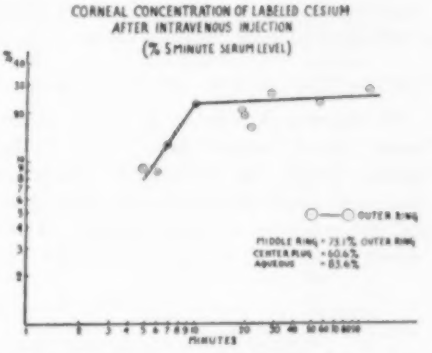

Fig. 7 (Potts and Johnson). The values of the outer rings plotted against time on logarithmic coordinates.

TABLE 6

RELATIVE CONTENT OF LABELED IONS BY CORNEAL RINGS AND AQUEOUS

Ion	Mean % of Outer Ring ± Standard Error of Mean			
	Outer Ring	Middle Ring	Center Plug	Aqueous
Iodide	100%	63.2±6.2	61.3±6.2	58.7± 2.7
Phosphate	100	45 ±7.2	33 ±6.1	82 ±10.9
Cesium	100	73 ±7.9	60.5±8.7	83.6±12.3
Sodium	100	38	31	100 ca.

this fact impossible. It should be noted that there is a definite tendency for the difference between the corneal regions to decrease as time goes on and as the animal approaches more nearly to equilibrium with the tracer. This is best shown by the figures for phosphate where the first seven values for the middle ring average 28 percent of the outer ring figures and the six longer-time middle rings average 65 percent of the outer ring, a difference of more than two times.

CONTRIBUTION OF THE AQUEOUS HUMOR

To separate, if possible, the effect of the limbal plexus supply from that of the aqueous supply, the silver-nitrate cauterization experiments described above were done and the results of a typical experiment are shown in Table 7. It can be seen that the aqueous content was lowered by the procedure. Although the aqueous content was dropped by some 30 percent, the contents of the corneal rings fell in the experimental eye by more than twice this much as compared with the control eye.

This is good evidence that the central corneal regions are largely dependent upon the limbal plexus for their supply of inorganic ions. If this were not true, both aqueous and corneal rings should have dropped by the same percentage.

To evaluate more directly the role of the aqueous in corneal supply, the results of injection of labeled material into the anterior chamber should be considered. Some typical experiments are presented in Table 8.

It can be seen that, after 10 minutes, a

TABLE 7

CORNEAL CONTENT OF LABELED PHOSPHATE AFTER INTRAVENOUS INJECTION WITH AND WITHOUT $AgNO_3$ CAUTERIZATION OF THE LIMBUS

	Normal Control Eye	Peritomy then $AgNO_3$ to Limbus
Rabbit weight, Kg.	2.1	
Total dose, c/m	4.28×107	
Total dose, P mg.	1.6	
Time of enucleation, min.	21	21
Tissue concentration, c/m/gm.		
Cornea		
Outer ring	5,930	2,160
Middle ring	1,760	800
Center plug	1,450	462
Aqueous	3,370	2,223
% 5 minute serum level		
Cornea		
Outer ring	9.20	3.38
Middle ring	2.73	1.24
Center plug	2.25	0.72
Aqueous	5.22	3.45

small but definite proportion of the injected material has found its way into the cornea. The concentration of activity in each cornea varies from one fourth to one half that in the aqueous and corresponds roughly to that found in the previous experiments, when one considers that corneal concentration resulted after a rising aqueous content, this after a falling one.

TABLE 8

CORNEAL CONTENT OF LABELED IONS AFTER INJECTION INTO THE ANTERIOR CHAMBER

	Iodide	Phosphate	Cesium
Volume injected, mm.³	1.72	0.86	0.86
Total activity, c/m	1.87×10^5	6.25×10^4	7.34×10^4
Total salt, mμg.	1.72 (NaI)	138	13,000
Length of experiment, min.	10.4	10.0	12.0
Estimated initial concentration of anterior chamber, c/m/cc.	9.84×10^4	2.50×10^5	2.94×10^4
Tissue content, c/m/gm.			
Cornea			
Outer ring	233,800	86,000	82,000
Middle ring	112,000	102,000	107,000
Center plug	139,000	103,000	112,000
Aqueous	618,000	176,400	152,000
Tissue content (percent total dose)			
Cornea			
Outer ring	4.53	0.82	3.27
Middle ring	1.80	0.70	3.66
Center plug	1.11	0.53	2.07
Aqueous	66	14.2	45.6
Tissue content, mμg.			
Cornea			
Outer ring	19.2	1.13	432
Middle ring	7.72	0.97	484
Center plug	4.77	0.73	274
Aqueous	262	19.5	5,900

It is worth noting, too, that in 2 of the 3 experiments cited the concentration of the corneal zones is higher at the center than at the periphery. Some experiments with the injection of fluorescein into the anterior chamber showed us that before mixing in the anterior chamber was complete, there were a number of convection patterns which allowed local high concentrations to be created for a matter of seconds. This can explain the variable results in the iodide experiment.

The results also indicate that all parts of the endothelial surface are equally permeable to the ions tested. There is no evidence that ions from the aqueous must migrate to the endothelial margin at the limbus in order to enter the cornea.

SUBCONJUNCTIVAL INJECTION

It was of interest to us to evalute the possibility that the whole conjunctival surface was an absorptive area feeding the limbal zone. To help do this, subconjunctival injections of about 1 mm.³ were made with the microsyringe near the limbus and, after freezing, the cornea was cut into four strips of equal width designated A to D, all parallel to the limbal tangent at the injection site. Two such experiments are cited in Table 9. They both show that, whereas the first strip adjacent to the site of injection acquires a small amount (0.5-percent ca) of the injected material, the rest of the cornea gets virtually none. At least for the substances in question, the subconjunctival path seems to need no consideration.

ANTERIOR SUPPLY

Two factors must be evaluated in considering the entrance of substances through

TABLE 9

CORNEAL CONTENT OF LABELED IONS AFTER SUBCONJUNCTIVAL INJECTION

	Phosphate	Cesium
Volume injected, mm.³	0.86	0.86
Total activity, c/m	7.72×10^{4}	7.65×10^{4}
Total salt, mμg.	138	13,000
Length of experiment, min.	60	31
Distance from limbus, of injection site, mm.	2	2
Corneal content, c/m/g		
Strip A	18,730	23,100
B	472	2,475
C	206	1,135
D	96	1,075
Corneal content, % total		
Strip A	0.450	0.360
B	0.001	0.064
C	>0.001	0.044
D	Negligible	0.025
Corneal content, mμg.		
Strip A	0.62	46.7
B	0.002	8.3
C	0.001	5.7
D	>0.001	3.3

the epithelial surface. The first of these is the concentration of the substance in question that is presented to this surface, and the second is the actual permeability of the corneal epithelium to the specific substance. The second aspect has received the undivided attention of many capable investigators and the results of three of our typical experiments presented in Table 10 make no startling contribution to the already expansive literature. They show that, for the inorganic ions measured, both positive and negative, there is a small but measurable pentration of the epithelial surface in 10 minutes, resulting in a concentration of 0.02 to 0.30 percent of the outside value in the corneal plug directly under the applicator. The rest of the cornea had negligible activity.

The first mentioned aspect, that of the concentration of intravenously administered substances in the tears, has been much less extensively investigated. Our determinations and the corresponding blood levels are presented graphically in Figure 8.

Of the three ions investigated, each shows a distinctly different type of behavior. The cesium content of tears in two determinations after intraveneous administration was 17 percent and 47 percent of the blood level at the time of collection in two determinations. The phosphate content was two whole

TABLE 10

PENETRATION OF EPITHELIAL SURFACE OF CORNEA BY LOCALLY APPLIED LABELED IONS IN ISOTONIC NEUTRAL SOLUTION

	Phosphate	Iodide	Cesium
Concentration of compound, mg/cc.	0.412	0.050	1.50
Activity, c/m/cc.	3.92×10^{6}	1.35×10^{7}	1.95×10^{6}
Length of exposure (min.)	10	10	10
Corneal plug			
Exposed to solution, c/m/gm.	14,600	11,060	5,420
% concentration of applied solution	0.37	0.02	0.28

orders of magnitude lower than this, a mere 0.3 percent, and this despite the fact that the lacrimal glands in the animal had phosphate contents almost exactly equal to the blood concentration.

Most unusual of all, the iodide content of tears after intravenous administration of I^{131} ranged from 170 to 300 percent of the blood level at the time of collection.

ent, for here by injection one labels the entire blood stream. In the case of the 29-minute P^{32} eye, for instance, the injected activity labeled some 6.0 mg. of phosphorous circulating in the blood so the corneal content of 56,000 counts per minute represents 1.34 μg. of phosphate that has entered the cornea in the experimental period—approximately 1,000 times as much as in the iodide

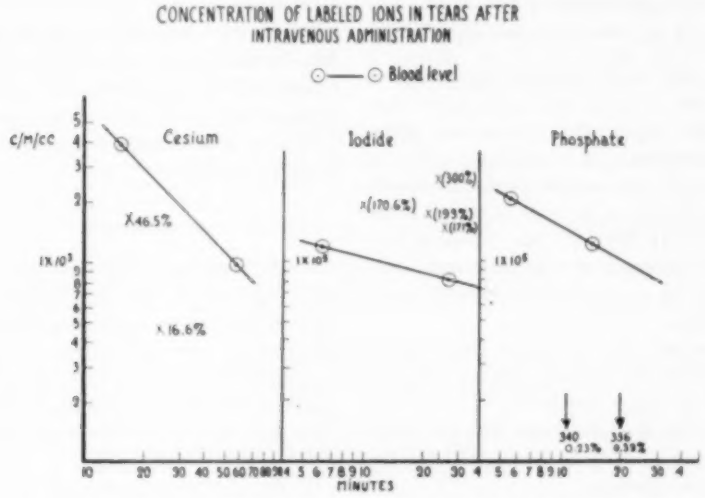

Fig. 8 (Potts and Johnson). Graph showing concentration of labeled ions in tears.

Discussion

For purposes of orientation it is important to establish the fact that the weights of materials which we have been following to the eye by diverse paths have been very small indeed. For this reason, absolute values have been given in Tables 8 and 9 and it is seen that the units are millimicrograms (mμg.).

Similar calculations for the intravenous experiments give similar orders of magnitude for the trace elements. One iodide experiment gave a total corneal content of 6.0 mμg., 13 minutes after injection.

The case of ions occurring in high concentrations in the blood is somewhat different, for here by injection one labels the entire blood stream. In the case of the 29-minute P^{32} eye, for instance, the injected activity labeled some 6.0 mg. of phosphorous circulating in the blood so the corneal content of 56,000 counts per minute represents 1.34 μg. of phosphate that has entered the cornea in the experimental period—approximately 1,000 times as much as in the iodide experiment.

These facts are emphasized for two reasons: (1) Because we wish to point out that these experiments in no way invalidate the generally accepted idea that inorganic ions permeate the cornea at a relatively slow rate in comparison to some compounds—organic solvents for instance; (2) since we have demonstrated individual physiologic personalities on the submicro scale for the various ions we have studied, we should emphasize the fact that, if nutritional deficiencies do play a part in corneal disease, they will involve substances whose transport is on just such a minute scale—vitamins, coenzymes, trace ions, and the like—and

generalizations from milligram-scale determinations will not necessarily be valid or useful.

The theoretical treatment of the rate of disappearance of radioactivity from the blood will not be considered extensively at this time. Suffice it to say that the logarithmic plot allows for convenient linear interpolation and that at least one type of blood curve has lent itself to expression as the sum of two exponentials:

$$C = 30\ e^{-0.693t} + 21\ e^{-0.1t} + 4$$

At this time there is a great temptation to assume with Merrell and associates[13] that each of the exponential expressions given above represents a separate diffusion process, each of which proceeds simultaneously. However, in view of the evidence accumulated by Hevesy[9] that diffusion into each tissue proceeds at a separate rate, such an assumption seems likely to prove an oversimplification.

At all events, with an exact expression for rate of loss from the blood, we are one step closer to an exact expression for rate of entry into the eye, and exact biologic counterparts may actually be established for the mathematical findings.

Some properties of interest come to light when one compares the rate of entry into the cornea of the ions studied with their rate of loss from the blood—presumably a measure of their rate of entry into the other tissues.

Iodide shows a flat blood-curve. From this one would expect a relatively low rate of entry particularly when the five-minute blood level, the basis of comparison, remains high. Nevertheless the plateau for iodide averages 45 percent of the five-minute blood level.

On the other hand, phosphate enters the tissues rapidly and has a relatively low five-minute blood level for a given dose despite the fact that this requires movement of all the labeled plasma phosphate. In the cornea, on the other hand, phosphate enters slowly and the outer ring plateau value is the lowest of the four ions. Cesium leaves the blood even more rapidly than phosphate and shows a plateau intermediate between phosphate and iodide.

From these observations one is forced to conclude that entry of ions into the cornea is governed by conditions other than those which control the loss from the blood stream into the large mass of tissue and that, further, each ion so far studied acts in an individual manner.

We do not mean to imply that generalizations in the future on an adequate amount of data will be impossible. We simply wish to state that at the present time generalizations from other tissues to the cornea are not likely to be correct.

Summary

1. Methods have been described for tracing the entry of ions into various corneal regions after intravenous intraocular subconjunctival and topical administration. The concentration of these ions in pilocarpine-stimulated tears has also been determined. The ion species used were phosphate, sodium, iodide, and cesium.

2. The disappearance from the blood of intravenously injected ions has been found to give a series of straight lines when blood level is plotted as time on logarithmic coördinates.

3. The rate of disappearance from the blood has been characteristically different for each of the four ions tested.

4. When the rate of entry into the cornea is expressed as percent of five-minute serum level, each of the four ions tested shows a different and characteristic pattern.

5. When rate of ion entry from the blood stream into concentric circular corneal regions is determined, the outermost region has a significantly higher concentration of the measured substance than the more interior regions. This indicates that the limbal vascular plexus plays a predominant role in supplying the materials investigated to the

cornea. When this plexus is damaged by silver nitrate, the concentration of injected ions in the cornea is drastically decreased.

6. A small but significant amount of the substances studied can pass through the anterior or posterior corneal surfaces. The passage through the endothelium may be made anywhere and is not restricted to the limbal zone.

7. The concentration of the substances in tears varies from 0.2 percent to 300 percent of the blood level. This fact must be combined with quantitative knowledge of the permeability of the epithelial surface before the role of the anterior route of supply can be adequately evaluated.

8. Subconjunctival injection allowed only a small proportion (0.5-percent ca) of the injected ions to enter the cornea and this entry was confined to an area quite close to the site of injection.

9. Substances such as the ions studied which enter the cornea in relatively low concentrations have individual and distinctive physiologic properties which must be taken into account before an adequate evaluation of corneal nutrition can be made.

University Hospitals (6).

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Discussion

Dr. Frank Vesey (New York): May I ask Dr. Potts, after this very interesting presentation, to make further investigations on animals that have a structure of Schlemm's canal, such as apes. We know the lower animals do not have that structure. It may turn out that Schlemm's canal was an organ of nutrition primarily, and not an organ of filtration, as it is generally accepted today.

Dr. David Cogan (Boston): I would like to offer a suggestion. I am very much interested in this paper, and I think the authors were very charitable to us.

I would like to suggest, however, that the title be changed from "Nutritional supply of corneal regions" to "The electrolyte movement in the cornea," as I think none of this fluid movement in the cornea necessarily indicates what happens in the nutrition of the cornea.

As for the difference in our findings and

the authors', chiefly in their conclusion that the endothelium was relatively permeable throughout to electrolytes and the epithelium to a less extent, that is contrary to our findings based on a chemical test and also based on the impedence of electric current by these membranes.

I presume the authors have thoroughly washed off the samples and have some evidence that all the radioactive material was removed from the surface before they measured their corneal buttons. I don't know just how one would prove that all the radioactive material was washed from the surface. I suppose one could use different time periods and demonstrate the electrolytes diffusing into the stroma if the membranes were permeable; whereas, they would remain adhering to the surface if it was a matter of incomplete washing.

From the first observations I inferred that the material did come from the limbus, there was always a higher amount at the limbus than in the central plugs. I thought that was compatible with the idea that it came from the limbus and not through the endothelium, especially since the aqueous content of the particular radioactive electrolyte was quite high.

Later observations, however, indicated that the electrolytes were roughly the same throughout the entire cornea, and it certainly looks as though it came through the endothelium. If it wasn't a contaminant I wonder if the manipulation during the injection, or the changes in the pressure within the eye, didn't alter the permeability of the endothelium enough to let the material go through.

In other words, there seems to me to be a contradiction between the first experiments, where there was a high concentration in the aqueous, which apparently had come there via the blood, and yet the cornea showed a much greater amount toward the periphery, and the subsequent observation of the injection into the anterior chamber where the substances were approximately equal in all parts of the cornea.

Dr. Jonas S. Friedenwald (Baltimore): In regard to the problem of what light these experiments throw on the permeability of the corneal surfaces, and more remotely and perhaps more importantly on the nutrition of the different fractions of the cornea, it seems to me important that these experiments should be carried further, to the end that after exposing the surface of the cornea to these solutions and separating various buttons, the epithelium might be scraped off and tested separately.

It may well be that substances penetrate into the epithelium but do not penetrate from the epithelium into the stroma, and it may be equally true that substances penetrate into the endothelium but not from the endothelium into the stroma. The precise localization of the boundary of impermeability in Dr. Cogan's experiments appears to be not between these cellular layers and the surrounding fluid, but between these cellular layers and the stroma.

Dr. David Cogan (Boston): May I mention one more point? The most important thing that I arose to say, I forgot, and that is that we measured the permeability of the cornea to radioactive sodium and radioactive iodine in Diodrast. Dr. Kinsey and I, when he was working with Dr. Bárány, had some Diodrast left over, and we made a few sporadic tests with it. I don't remember that we tried electrolytic iodine. All of the experiments showed that in our in vitro preparations none of the radioactive sodium or Diodrast came through, as long as the epithelium was intact.

Dr. Albert M. Potts (Cleveland): Regarding Schlemm's canal, we would be happy to do such experiments if the animals were available. It represents a financial problem to us, at this time insurmountable. However, if we are ever able to do such experiments we shall certainly be interested in the investigation of whether Schlemm's canal is a possible organ of nutrition rather than a sewage canal.

The question of the nutritional supply that

Dr. Cogan brought up doesn't seem to me to show contradiction between the two sets of experiments. In the case of the intravenous experiments, it was noticed that the level of the aqueous was very near that of the middle ring and the center plug. It hovered around that central area. Even so, our experiments demonstrated that when material was injected into the anterior chamber, the concentration in the cornea was not equal to that of this artificial aqueous that was created, but on the order of 0.2 percent of the concentration in the artificial aqueous, so such an inflow would never show up on an intravenous experiment where the aqueous was equal in level to the middle ring and the center plug. The concentration in the outer ring was always higher than that of the aqueous. The rings in the center were very nearly the same.

However, if one were able completely to block the supply from the limbus, as we were unable to do (this completeness of block is something that requires a finer anatomic technique than silver-nitrate cauterization), then we might expect that the level in the whole cornea might correspond to something like 0.2 percent of the level in the aqueous.

As far as having the material adsorbed on the surface was concerned, we were able in some cases, since these pieces were frozen, actually to scrape the endothelial surface with a scalpel, and we were able to notice no serious loss of the activity that was transferred in the intraocular-injection experiments. We believe there actually is something that has gone in, but it must be noted that this amount is small, and when an intravenous supply also exists, that amount is completely masked.

In regard to Dr. Friedenwald's statement, we would very much like to do such experiments. The sort of thing we dreamed up was a freezing microtome which could be oriented so that it would be exactly at right angles to the surface of these rings and plugs, and to make sections not only removing the epithelium but also at different depths through the stroma itself. This is a mechanical project which is going to the manufacturer who made our syringe, but it has been postponed for a while.

As far as the title is concerned, we intend this paper to be only the first of a series of papers, and it is true we are measuring diffusion of ions. This is simply a dry run, as it were. We hope to measure the diffusion of nutrients in the future.

Ophthalmic Miniature

Heliodorus asserted: "Love offers proof that the eyes find a passage to the soul and it is not difficult to assign the reason for this; of all inlets to our senses, the sight is the most lively and most varied in its emotions, and if some give the stroke of the evil eye unconsciously to those they love, how much more must the effect be when malignant will is added to the force of nature."

Cited by Burton, *Anatomy of Melancholy*, 1652.

STUDIES ON THE PHYSIOLOGY OF THE EYE USING TRACER SUBSTANCES*

PART III. FURTHER STUDIES ON THE STEADY-STATE RATIO OF SODIUM BETWEEN THE PLASMA AND AQUEOUS HUMOR IN THE GUINEA PIG AND MONKEY

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In a previous study[1] utilizing radiosodium (Na^{24}) as a tracer, we reported the steady-state ratio of the sodium of the plasma water to sodium of the aqueous to be 0.920 in the guinea pig. It was suggested at that time that this large excess of sodium in the aqueous over that in the plasma water of the guinea pig might be due to the passage of water from the aqueous through the cornea to the tears with the consequent concentration of sodium in the aqueous. It was also pointed out that this low plasma-aqueous ratio for sodium in the guinea pig might be evidence for the presence of a secretory mechanism which is absent in other species.

The present work is concerned with investigating the possibility that the sodium of aqueous of the guinea pig is concentrated by the passage of water outward through the cornea to the tears and with studying the steady-state ratio in another species, the monkey. The methods used in the previous study were further refined for this investigation.

METHODS

Radioactive sodium (Na^{22}) was prepared in the 60-inch cyclotron of the Department of Terrestrial Magnetism, Carnegie Institution of Washington. Magnesium (Mg^{24}) was bombarded in the cyclotron with 16 million electron volt deuterons (D) with the following reaction:

$$_{12}Mg^{24} + {}_{1}D^{2} \rightarrow {}_{11}Na^{22} + {}_{2}He^{4}$$

The radiosodium (Na^{22}) was separated chemically from the magnesium and the sample was assayed by radioactive methods for the purity and concentration of its radiosodium.

The guinea pigs were of mixed sexes, weighed between 500 and 1,000 gm. and were fed rabbit pellets and fresh greens. Friedenwald and co-workers[2] have shown that vitamin-C deficient guinea pigs may have a lowered rate of formation of intraocular fluid. As a precaution against vitamin-C deficiency in our guinea pigs about half received 50 mg. of ascorbic acid every other day for two weeks prior to the experiment. There was no evidence of vitamin deficiency in either group and no difference between the two groups in the experimental results.

The monkeys were young adolescents of mixed sexes and weighed approximately three kg. They were fed a mixture of wheat, soy beans, and dried milk which was fortified with vitamins A, C, and D. They were healthy, normal animals which had been inoculated with poliomyelitis virus but had not become infected.

The experiments were performed in a similar manner on both the guinea pigs and monkeys. The animals were injected intraperitoneally with 0.75 cc. per kg. of a solution containing about 4.0 mM/cc. of radiosodium (Na^{22}) and with a radioactivity of 4.0 microcuries per cc.

After 24 hours, the animals were etherized briefly and a sample of aqueous was removed with a calibrated micropipette. A Kinsey pipette was used to draw the aqueous from the monkey while still smaller pipettes were used to draw the aqueous from the guinea pig. The sample was adjusted to one of the calibration lines and

* From the Wilmer Ophthalmological Institute of The Johns Hopkins University and Hospital and the Carnegie Institution of Washington, Department of Embryology, Baltimore. Presented at the 18th scientific meeting of the Association for Research in Ophthalmology, Inc., Philadelphia, June, 1949.

TABLE 1

OPEN-LID VERSUS CLOSED-LID EYES
STEADY-STATE RATIO OF SODIUM OF WATER OF PLASMA/SODIUM OF AQUEOUS
Guinea Pig

No.	Type of Eye	Pe† μM Na*/kg. H_2O	Ae‡ μM Na*/kg. H_2O	Pe/Ae
5	open	7.305	7.327	0.997
	closed		7.400	0.988
6	open	3.011	2.957	1.018
	closed		2.971	1.013
7	open	4.993	5.183	0.963
	closed		5.162	0.967
8	open	3.891	3.949	0.985
	closed		3.869	1.005
9	open	3.036	3.183	0.954
	closed		3.101	0.979

* Na = sodium tagged with Na^{22}.
† Pe = concentration in plasma of *Na when aqueous is at equilibrium in the plasma.
‡ Ae = concentration of Na^{22} in aqueous at equilibrium.

then delivered to a small disc of filter paper which had been previously cemented* to the center of a copper disc. The sample was spread evenly over the filter-paper disc.

To assure the same absorption of radioactivity from the plasma and aqueous samples, the same amount of nonradioactive plasma was added to the aqueous samples as was used for the plasma determinations.

Immediately after the sample of aqueous was removed, blood was taken by cardiac puncture. Samples of the plasma or serum were measured in the same pipette as the aqueous and were adjusted to the same calibration line as used for the corresponding sample of aqueous. These samples were also delivered onto filter-paper discs cemented on copper. An equal amount of water was added so that a similar amount of water and plasma protein was present on both the aqueous and plasma discs. The samples were allowed to dry at room temperature. Measurements of the radioactivity of the samples were made with a Geiger-Müller tube and scaling circuit. The radioactivity of the samples was converted into micromoles of tagged sodium.

The amount of water in the guinea pigs' plasma was determined by drying weighed samples of plasma and subtracting the weight of the residue. The solids were found to be 5 percent of the total weight. The amount of water in the monkeys' serum was measured in the same manner and was found to have approximately 8 percent of solids. The error involved in assuming the aqueous to be entirely water is less than 0.5 percent and consequently no correction was made for its salt content.

*Multi Lok diluted with toluene.

EXPERIMENTS AND RESULTS

Three separate sets of experiments were performed utilizing these techniques.

a. The steady-state ratio of the sodium of the plasma water to sodium of the aqueous in guinea pigs which had one set of eyelids closed for 24 hours prior to the removal of the samples.

This closed-eye experiment was concerned with the role of the cornea in water transfer from the aqueous. In this series of animals one eye of each animal was clipped shut using two wound clips. Care was taken to approximate the lid margins equally. This afforded complete closure of the lid and, when the lids were opened 24 hours later, no damage to the cornea was observed.

The experiment was so designed that the

"open eye" would function in a normal manner with the tears passing over the cornea and evaporating to the outside atmosphere. On the other hand, the tears could not evaporate from the opposite or "closed eye" because of the closed lids. Steady-state studies were done on these animals with exactly the same procedure described above.

In Table 1 the steady-state ratio of the sodium of the plasma water to the sodium of the aqueous is compared in the "open" and "closed" eyes of the guinea pig. It is seen that there is no significant difference in the steady-state ratio between these two types of eyes.

TABLE 2

STEADY-STATE RATIO OF SODIUM OF WATER OF PLASMA/SODIUM OF AQUEOUS

Guinea Pig

No.	Pe† μM Na*/kg. H_2O	Ae‡ μM Na*/kg. H_2O	Pe/Ae
1	4.307	4.410 4.318	0.977 0.977
2	5.979 6.102	5.972 5.894	1.001 1.035
3	5.195	5.407 5.426	0.960 0.957
4	5.177	5.499 5.208	0.941 0.993
5	7.305	7.327	0.997
6	3.011	2.957	1.018
7	4.993	5.184	0.963
8	3.891	3.949	0.985
9	3.036	3.183	0.954
10	6.545	6.754	0.969
11	6.031	6.352	0.949
12	5.927	5.806 5.878	1.021 1.008
13	6.501	6.368 6.713	1.020 0.968
14	6.153 6.042	6.542 6.619	0.941 0.193
15	5.178	5.386 5.502	0.961 0.941
			X = 0.977 ± = 0.0055

* Na = sodium tagged with Na^{22}.
† Pe = concentration in plasma of *Na when aqueous is at equilibrium in the plasma.
‡ Ae = concentration of Na^{22} in aqueous at equilibrium.

b. The steady-state ratio of the sodium of plasma water to sodium of the aqueous in the normal guinea pig.

The average steady-state ratio of the sodium of the plasma water to sodium of the aqueous of the guinea pig was 0.977 ± 0.0055 (table 2).

c. The steady-state ratio of the sodium of the plasma water to sodium of the aqueous in monkeys.

The average steady-state ratio of the sodium of the plasma water to sodium of the aqueous of the Macacus rhesus was 1.15 ± 0.014 (table 3).

TABLE 3

STEADY-STATE RATIO OF SODIUM OF WATER OF PLASMA/SODIUM OF AQUEOUS

Monkey

No.	Pe† μM Na*/kg. H_2O	Ae‡ μM Na*/kg. H_2O	Pe/Ae
1	1.092	0.972 0.969	1.123 1.127
2	1.059	0.908 0.904	1.166 1.172
3	1.039	0.951 0.978	1.093 1.062
4	1.212	1.076 1.044	1.127 1.161
5	1.130	0.903 0.951	1.251 1.188
6	0.971	0.907 0.935	1.071 1.038
7	1.411	1.122 1.206	1.257 1.170
8	1.151	0.994 0.929	1.157 1.239
9	4.442	3.807	1.167
			X = 1.150 ± = 0.014

* Na = sodium tagged with Na^{22}.
† Pe = concentration in plasma of *Na when aqueous is at equilibrium in the plasma.
‡ Ae = concentration of Na^{22} in aqueous at equilibrium.

Discussion

The cornea is permeable in both directions to water,[3] and we previously suggested that the excess of sodium in the guinea-pig aqueous might be due to the passage of water out through the cornea to the tears with the subsequent concentration of sodium in the aqueous. The closed-lid experiment was designed to test the effect of the evaporation of the tears on the concentration of sodium in the aqueous. There was no significant difference between the steady-state ratio of plasma to aqueous in these "closed eyes" and the normal "open eyes."

It is concluded from these experiments that there is no significant loss of water from the aqueous through the cornea due to the increased osmotic pressure of the tears exposed to drying in the "open eyes."

In our previous report on the steady-state ratio of sodium between the plasma and the aqueous of the guinea pig[1] we reported a ratio of 0.920 ± 0.033. We used a short half-life radiosodium (Na^{24}) and measured the quantity of aqueous and plasma gravimetrically. In the present study, using a long half-life radiosodium (Na^{22}) and a more accurate volumetric method to measure the quantity of the sample, the steady-state ratio was found to be 0.977 ± 0.0067. Both studies indicate an excess of sodium in the aqueous of the guinea pig relative to that in the plasma water.

To our knowledge there is no experimental value for the ratio of the total plasma sodium to the dialyzable plasma sodium in the guinea pig. An excess of sodium in the plasma over that of the dialysate is to be expected on the basis of the Donnan factor and possibly also because of the decreased sodium activity in the presence of proteins (bound sodium of Green and Powers[4] and Ingraham, Lombard, and Visscher[5]). We performed preliminary experiments to measure this ratio.

Guinea pigs were injected intraperitoneally with radiosodium four days prior to removal of plasma. The blood was drawn under oil, allowed to clot, and centrifuged, and the serum was placed in a cellophane sack. The sack was then placed in approximately isotonic buffered Locke's solution in a tube in a desiccator. The desiccator was filled with a mixture of 5-percent carbon dioxide in nitrogen. A capillary column was tied into the sack and the pressure of the plasma adjusted to compensate for the plasma protein osmotic pressure.

Aliquots of the Locke's solution and plasma were analyzed for radiosodium after 24 hours, using the copper-disc techniques and a Geiger counter in the manner already described. A similar experiment was performed in which the radiosodium (Na^{22}) was added to normal guinea-pig serum in the sack and the experiment was then performed as has been described.

There was a 5 to 8 percent excess of sodium in the plasma water. This excess of 5 to 8 percent represents the total excess of sodium in the plasma water versus the plasma dialysate and at least part of this excess is to be attributed to the Donnan factor. More carefully controlled dialysis experiments are necessary to determine the exact value of the Donnan factor.

In determining whether or not the aqueous of the guinea pig is similar to, or different from, a dialysate, the evidence from our *in vivo* and *in vitro* experiments points to a total excess of over 7 percent of sodium of aqueous over sodium of plasma dialysate. This indicates that sodium is probably secreted into the aqueous of the guinea pig.

Our studies of the steady-state ratio of sodium between the plasma water and aqueous of the monkey show a distinctly higher ratio than we found in the guinea pig. At present we are unable to explain this difference.

Summary

1. Radiosodium (Na^{22}) was used as a tracer to study the distribution of sodium between the plasma and aqueous of the guinea pig and of the monkey (Macacus rhesus).

2. The increased osmostic pressure of the tears exposed to drying in the normal guinea pig's eyes does not cause a significant loss of water from the aqueous through the cornea.

3. The steady-state ratio, sodium of the plasma water to sodium of the aqueous, was found to be 0.977 ± 0.0055 in the guinea pig. In the guinea pig there is over a 7-percent excess of the sodium of the aqueous over that of the sodium of the plasma dialysate.

4. The higher concentration of sodium in the aqueous, compared with the sodium plasma dialysate in the guinea pig, points to the probability that sodium is secreted from the plasma into the aqueous of this species.

5. The steady-state ratio, sodium of the plasma water to sodium of the aqueous, was found to be 1.15 ± 0.014 in the monkey (Macacus rhesus).

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Discussion

Dr. V. Everett Kinsey (Boston): I have performed similar experiments on guinea pigs using ordinary analytical techniques and have confirmed the results reported by Dr. Scholz. In rabbits, my results were similar to those obtained by Dr. Scholz in the monkey.

DETACHMENT OF THE RETINA IN YOUNG ADULTS*

An analysis of the treatment of a young age group at an Army General Hospital

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The successful treatment of detachment of the retina has only been realized within the past 20 years. It was in 1929 that Jules Gonin first described his method of sealing retinal tears and evacuating subretinal fluid by means of a galvanocautery. Safar, Weve, Larsson, and others then developed the diathermy methods of treatment, variations of which are employed today. Chemical cauterization was first advanced by Guist, and Lindner and Pischel were responsible for reviving interest in the scleral resection operation.

At the time of World War I, there was, therefore, no satisfactory method of treatment for detachment of the retina. World War II, however, came in an era when the successful treatment of such cases was by no means an uncommon event. An opportunity was offered to study the results of operative treatment of retinal detachments in a young age group accumulated over a relatively short period of time.

In civilian practice the average case of retinal detachment falls into the age group of 50 to 60 years.[1] A critical study of the age group presented in this paper would enable one to compare and contrast these observa-

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tions with those derived from the analysis of detachments acquired at an older age.

Serious ophthalmologic cases were sent to a few general hospitals designated as "Army Eye Centers," which made possible the accumulation of a number of cases of this condition. No attempt has been made to compare one operation with another because so many different ophthalmologists were responsible for the various operations. The following report is presented as a statistical survey of the outcome of those cases.

General statistics

a. Source of material. A group of 80 unselected cases is analyzed. Beginning in January, 1945, and ending in January, 1948, 139 operations were performed on this group by 18 different physicians. An operation was considered successful when a complete attachment of the retina was obtained. However, it should be mentioned that in two of the 80 cases a very small area of detachment still remained. These two cases were considered in the successful category,[3] because the areas were completely surrounded by induced choroidal reaction.

b. Age group. There were 14 patients between the ages of 17 and 19 years; 48 patients from 20 to 29 years; 14 patients in the 30- to 39-year-old group; and only four patients from 40 to 49 years of age.

c. Sex. Of the 80 patients, 77 were male and three female.

d. Race. Seventy-six patients were white and four were Negro.

e. Trauma. There were 50 cases due to injuries and 30 nontraumatic cases. Thirty of the 50 traumatic cases (60 percent) were battle injuries, 26 being penetrating wounds.

f. Technique of operation. A total of 139 operations were performed. Electrocoagulation by means of the Liebel-Flarsheim unit was the most frequently employed method although the Lacquererre electrode was used occasionally in the period from January, 1945, to March, 1946. On six separate occasions the ball electrode was employed when the size of the retinal rent was very extensive. In all, 120 operations were performed using the electrocoagulation method.

A total of eight scleral resections, four electrocoagulations with scleral trephination, and three Guist procedures comprised the remainder of the operations.

When indicated, the patients were kept in bed for one week prior to surgery. To induce nonoperative absorption of subretinal fluid, their eyes were either bandaged or covered with pinhole goggles. After operation, the patients were routinely kept with both eyes bandaged for a period of three weeks. In cases with a favorable result, pinhole goggles were then employed for a 2- or 3-month period. The patients were observed for 4 to 6 months after operation before final disposition was made.

Statistical observations

a. General. Of 80 operated cases, 45 (56 percent) were successful, and 35 (44 percent) were not successful.

b. Battle injuries. There were 30 such cases—10 (33 percent) in which the results were favorable and 20, unfavorable.

c. Penetrating injuries. Favorable results in these cases were infrequent. Of 28 cases, only nine (32 percent) were successful. In the group of *nonpenetrating wounds,* however, the results were more favorable. There were 52 cases with 36 (70 percent) reattachments.

d. Trauma. These cases were grouped as direct or indirect according to the method advocated by Knapp.[3] Table 1 illustrates the results obtained.

Among the 42 cases due to direct trauma were 28 cases of penetrating intraocular injury, which explains the low percentage of success in this category. In the average series of retinal-detachment cases, the incidence would not be so great since the patients would not have been subjected to wartime conditions.

e. Complicating uveitis. The diagnostic criterion for uveitis was the presence of

TABLE 1

OPERATIVE RESULTS OBTAINED IN 80 CASES OF RETINAL DETACHMENT

Type	No. Cases	Successful	Unsuccessful	% Success
Traumatic				
a. Direct	42	16	26	38
b. Indirect	8	6	2	75
Atraumatic	30	23	7	73

beam and cells in the anterior chamber and sometimes a fundus lesion. Vitreous floaters were, for the most part, discounted in establishing this diagnosis since they could be demonstrated in practically every case. There were 26 such cases, seven (27 percent) with a favorable outcome. Those cases without complicating uveitis comprised a group of 54, of which 38 (70 percent) showed successful results.

f. Cases without penetrating injury or complicating uveitis. Statistics in this group are more favorable since the complicating factors of penetrating injury and uveitis are absent. Of the 80 cases, 41 had neither of these two complicating factors, and the incidence of success was 83 percent (34 reattachments). When both penetration of the globe and uveitis were present, only four (27 percent) of the 15 cases were successful.

g. Disinsertions. A group of 27 proved cases was tabulated, of which 19 (70 percent) had successful outcomes.

h. Holes and tears. No attempt was made to classify the varieties and locations of the holes, tears, or disinsertions. A series of 29 cases demonstrated visible evidence of holes and/or tears. In 14 cases, there was reattachment after operation (48 percent). No attempt has been made to compare results in cases with holes to cases with tears. Only six cases gave visible evidence of a hole in the retina while 23 cases demonstrated a retinal tear. It was felt that no accurate conclusions could be drawn from analyzing such a group.

In the series of cases with holes, tears, and disinsertions, a visible dissolution in the continuity of the retina was noted in 56 cases or 70 percent of the total 80 cases. In the remaining 30 percent of cases there were many patients in whom an adequate view of the fundus for proper diagnosis was unobtainable due to dense vitreous opacities induced in particular by penetrating wounds.

i. Relation of time of origin to time of operation. These data can be most easily understood by consulting Table 2, which illustrates that the prognosis for success was better when the patient was operated soon after the origin of the detachment.

j. Incidence of success in relation to number of operations per case. An analysis of Table 3 indicates that prognosis was best in those cases which reattached after one operation.

k. Refractive error. Seventy-one patients were emmetropic. The criteria for emmetropia in this series was arrived at arbitrarily. Those patients whose refractive error fell within the plus-1 to minus-1 range were con-

TABLE 2

RESULTS IN RELATION TO TIME ELAPSING BETWEEN ORIGIN OF DETACHMENT AND OPERATION

Time	No. Cases	Successful	Unsuccessful	% Success
3 months	50	33	17	68
6 months	19	9	10	47
1 year	10	4	6	36
2 years	1	0	1	—

sidered emmetropic. Seven patients were myopic and two were hyperopic. Because of this small series of refractive errors, it was assumed that a statistical evaluation would be meaningless.

Types of operations

A total of 139 operations were performed upon the 80 cases. In 128 of these operations, electrocoagulation was employed, and, in four instances, in addition to electrocoagulation, a trephination was performed over the site of greatest detachment.

In only three patients was the Guist procedure tried, and then only as a last resort after the standard electrodiathermy had failed. The scleral resection operation was attempted in eight cases. Three were successful. Of the five unsuccessful results, three of the cases had been subject to at least one reattachment procedure prior to the scleral resection. In view of the small number of cases in this series, further analysis of these cases has not been carried out.

Discussion

Certain observations closely parallel those obtained in studying retinal detachments of an older age group.

1. The over-all incidence of success (56 percent) compares closely with the statement of Duke-Elder[4] that 50 percent of detachments can be cured.

2. The higher incidence of success obtained in cases of disinsertion as compared with holes and tears follows previous observations.[5-7]

3. The observation that the incidence of success falls off as the time between origin of detachment and time of operation lengthens is confirmed by the statistics herein presented.

4. By far the greatest number of successes resulted when the retinas became attached after the first operation.

Analysis of successes

The most striking observation was that, in the absence of both uveitis and penetrating ocular injury, the incidence of success was 83 percent in 41 cases. Although this certainly represents a very high number of successful reattachments, there are certain factors which in part explain this observation.

TABLE 3

Results in relation to number of operations

No. Operations	No. Cases	Successful	Unsuccessful	% Success
1	38	28	10	74
2	30	14	18	47
More than 2	12	3	9	25

Age must be considered a decisive factor for 77 percent of the cases were in the age group, 17 to 30 years. The blood supply to the retina and choroid in such a low-age group has undergone little, if any, degenerative change.

The blood supply of the choroid, including the lamina vitrea and the contiguous pigment epithelium of the retina,[8] is particularly affected by age. The walls of the vessels of the choriocapillaris become thickened. Hyalin degeneration may occur, which sometimes results in the complete obliteration of a vessel. The larger choroidal vessels, particularly the arteries, show varying amounts of degeneration.[9] The capillary net is much more irregular in elderly people, some vessels being almost occluded, while others exhibit compensatory dilation.

Maintenance of the vascular integrity of the choroid is necessary for the successful outcome of a detachment operation. The production of a satisfactory exudative reaction is the surgical objective. The later necessary absorption of these products of exudation, as well as the subretinal fluid, is a function

of the posterior uvea. This concept was stated very clearly by Arruga.[10] One might assume, therefore, that the presence of senile changes in the choroid would hamper the chances of operative success.

The nutrition of the retina likewise must remain undisturbed in order to obtain satisfactory results in treating retinal detachments. The retinal vascular changes found in an older age group were, for the most part, not encountered in this series.

Analysis of Failures

The two most striking causes for operative failure were the presence of (1) penetrating injury and (2) uveitis. When both of these complications were present, the incidence of success in 15 cases was reduced to 27 percent.

It is certainly not difficult to understand why operative prognosis should be poor in the presence of a retinal detachment secondary to a perforating ocular wound. Both extensive retinal and choroidal destruction predispose to failure. Then, too, the destruction of the vitreous, caused by a foreign body traversing the globe, may lead to the development of vitreous bands, which adhere to both choroid and retina and thereby increase the chance of operative failure.

Moreover, penetrating injuries predispose to uveitis, as evidenced by the fact that 16 of the 26 cases in which uveitis was present had a history of penetrating injury.

In view of the importance of maintaining the integrity of the choroid, it is easy to appreciate why the presence of uveitis may be responsible for operative failure. When the choroid cannot satisfactorily absorb either the subretinal fluid or the products of exudation induced by surgery the incidence of success is reduced.

Finally, in discussing reasons for failure, it should be mentioned that the inability to locate a hole, tear, or disinsertion reduced the chances for a successful outcome. This was the situation in 24 cases, 11 (46 percent) of which were successfully treated. On the other hand, visible evidence of dissolution in the retinal continuity was noted in 56 cases (70 percent of the total) with success in 60 percent.

Conclusions

A group of 80 unselected patients in a young age group, received a total of 139 operations for retinal detachment, with an over-all incidence of success in 56 percent of the cases.

The high incidence of success in those cases without severe complications is attributed principally to the healthy choroidal and retinal vasculature present in young persons. In addition, visible disruption in the retina (holes, tears, and disinsertions) were found in 70 percent of the cases.

Causes for failure were, for the most part, attributed to the complicating factors of uveitis and penetrating injury.

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STUDIES OF THE EYE WITH RADIOIODINE AUTOGRAPHS*

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Photographic techniques have been applied to tracer studies on the eye with radioactive sodium (Na^{24}),[1a,b] phosphorus (P^{32}),[2,3] and sulphur (S^{35}).[4] The suitable half life of radioiodine (I^{131}) and its availability suggested the use of radioautography to reinvestigate contradictory data on the distribution of iodine in the eye as reported in the old literature.[5-8] Furthermore, the problem of quantitative evaluation of radioautographs of the eye could be well studied with this labeled indicator. From a practical viewpoint the experimental results might add to the rationale of ocular iodine therapy.

MATERIALS AND METHODS

Young, mature, albino rabbits were used in the study. Radioactive inorganic iodine (I^{131}) was supplied by the Department of Radiological Research of the College of Physicians and Surgeons in the form of a solution of the carrier-free sodium salt. Radioautographs were made from fresh-frozen slices of the eye or from 10 micron paraffin sections according to the methods described[1] in the study of Na^{24} with minor modifications.

In the "macro" method slices were cut thinner (1 to 1.5 mm. instead of 2.5 mm. thick) in the later part of the study. In the "micro" method an attempt was made to substitute a dry freezing technique[9] for the fixation procedure using absolute alcohol or acetone prior to infiltration with paraffin in order to avoid loss of the indicator during fixation.

Frozen slices of the eye were dehydrated in vacuo, imbedded in paraffin, and cut. Under gentle heating, the sections were mounted on slides which had a thin coat of egg albumin. In conformity with the technique of Hamilton and co-workers[10] the sections and the film were kept in close contact for the time of exposure (about 10 days), then the two parts were separated for staining of the section and developing of the film (4½ minutes, Eastman Kodak developer D11, temperature 20°C.). The final preparation was obtained by superimposing and aligning the tissue landmarks with the corresponding details in the radiograph.

IONTOPHORETIC TRANSPORT OF RADIOIODINE

Technique. The labeled element was introduced through the cornea by cathode or anode iontophoresis (2 ma. 5 minutes) from a solution of radioiodide which had an activity of 100 microcuries per cc. Local anesthesia was induced with dibucaine hydrochloride (0.1 percent). The films were exposed 15 hours and developed four minutes.

Results. One or two hours after iontophoresis from the cathode, the cornea in the frozen slices gave the greatest photographic effect. The darkening of the film by radiations from the tracer in the iris was less marked but much more definite than that seen in the region of the anterior chamber. Under the conditions of the experiment almost no photographic effect was visible in the area of the posterior portion of the eye, except for a dim contour of darkening along the external coat (fig. 1). The outlines of the anterior part of the eye were faint in radiographs four hours after treatment. The film showed only a slight shading when the anode had been used as the active electrode for five minutes at two milliamperes one hour before enucleation.

There was a striking difference between the radiographs produced in an electric field

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by I^{131} and those produced by Na^{24} in a previous study (fig. 1). A homogeneous blackening of the photographic emulsion corresponded to the entire anterior chamber after introduction of Na^{24} by anode iontophoresis; whereas, selective darkening of the film along the walls of the anterior chamber characterized the radiographs in the experiments on cathode iontophoresis with I^{131}.

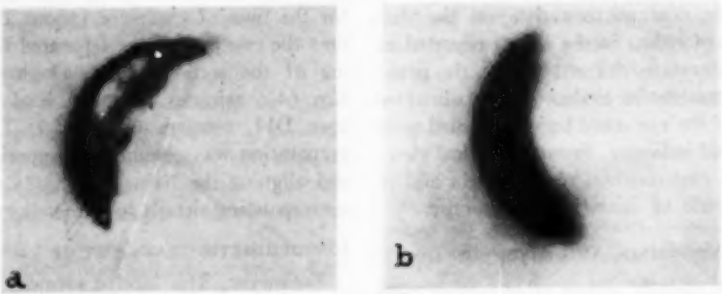


Fig. 1 (von Sallmann and Dillon). Radiographs of frozen slices of rabbit eyes two hours after corneal iontophoresis. (a) With I^{131}, (b) with Na^{24}.

Comment. The almost negative photographic results observed after anode iontophoresis, in contrast to the results obtained with cathode iontophoresis, indicated that true ion transfer of the radioactive indicator was the important factor in its penetration through the cornea. Damage of the corneal epithelium under the anode, allowing diffusion of the undissociated salt, had obviously a minor effect on penetration.

It was noted by Steindorff[8] that the amounts of iodine determined in the aqueous humor following iontophoretic introduction of relatively concentrated solutions of sodium iodide (two percent) at two milliampere for two minutes were low and varied greatly.

The autoradiographs suggested that the labeled compound was adsorbed to proteins within the anterior chamber. Erratic results must be anticipated because the protein content of the aqueous humor increases irregularly during the iontophoretic procedure. The concentration of radiotracer in the aqueous humor obviously could not provide information about the amount present in the walls of the anterior chamber.

Distribution of I^{131} in the eyes after systemic administration

1. General technique. The intraperitoneal route was chosen for systemic introduction of the tracer material into the rabbit. One millicurie of I^{131} was the usual dose and is equivalent to 0.0081 μg. The concentration of the radioisotope was one millicurie in 5 cc. of distilled water. The animals were killed by exsanguination from the heart, 1, 2, 4, 6, 24, or 48 hours after injection. Termination of the experiments by perfusion from the heart with Ringer's solution did not prove satisfactory for this type of experiment. Fourteen rabbits were used.

In a series of four rabbits the distribution of I^{131} was studied in eyes with corneal ulcers, and in eyes with experimental endophthalmitis. The corneal ulcers were laboratory infections of unknown etiology. Endophthalmitis was produced with an 18-hour broth culture of a pathogenic strain of Staphylococcus aureus in a dilution of 10^{-8}. An amount of 0.05 cc. was injected into the anterior chamber or 0.02 cc. into the vitreous space 20 hours before the animal was to receive the tracer dose. The eyes were removed 1 or 2 hours after injection.

2. Technique of densitometry on radio-

autographs of frozen slices of the eye. Light transmission was measured on a densitometer with an opening for the light of 0.34 mm. in diameter (fig. 2). The film with the radioautograph was fastened by strips of scotch tape on a slide and moved in close contact with the opening by means of a microscope mechanical stage equipped with Vernier scale. The instrument was combined with a sensitive electronic spot photometer with a direct reading density scale.* Thus diffuse density was determined by measuring all the emergent light.

3. Technique of correlating densities in the radioautographs to radiation values in calibrated standards. Frozen agar discs of proper dimensions were employed as calibration source. Radioiodine was added to a three-percent solution of agar and, after thorough mixing and cooling, discs were cut which measured 10 mm. in diameter and 2.5 mm. in thickness. The radioactivity of the tracer atoms dissolved in agar increased in arithmetic progression from 0.05 to 2 microcuries per cc. The content of I^{131} in the discs was measured in the G. M. counter in several instances.

The discs were then frozen in a carbon-dioxide-alcohol mixture and placed against ultra-speed X-ray dental film. Time of exposure and technique of development of the film were identical to that used for the radiographs of the frozen slices of eyes in the respective experiments. The photographic effect of the calibrated standards then served for the interpretation of the density readings of the radiographs from the eyes in terms of radioactivity.

Results

Radiographs of frozen slices of normal eyes enucleated one hour after intraperitoneal injection again revealed preferential localization of radioiodine in the cornea. At this time the periphery of the cornea seemed to contain more radioactive material than the central part. The accumulation of reduced silver granules along the landmarks of the anterior uvea and of the inner and outer coats of the posterior segment contrasted with the moderate darkening of the film in areas corresponding to the anterior chamber, vitreous space, and optic nerve. The lens did not have any effect on the film emulsion and appeared as a clear area in the autographs.

The distribution of darkened regions

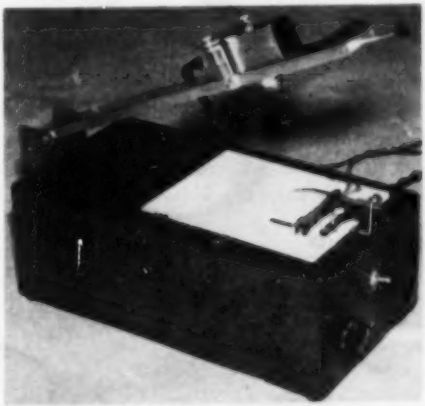


Fig. 2 (von Sallmann and Dillon). Densitometer used on radiographs.

showed a slight shift when eyes enucleated 4 and 6 hours after injection were examined. At the six-hour interval, a fine network pattern became visible in the vitreous part and the density of the film in the region of the optic nerve approached that of the neighboring structures. At the 24-hour interval these changes were accentuated and a distinct line of increased darkening was occasionally seen to correspond to the posterior surface of the lens (fig. 3).

The infiltrated parts of the ulcerous cornea caused more intensive darkening of the film so that it seemed that the labeled iodine was moderately concentrated in the area of infiltration. Endophthalmitis induced by inoculating the anterior chamber or the vitre-

* Photovolt photoelectric transmission densitometer with extended dial.

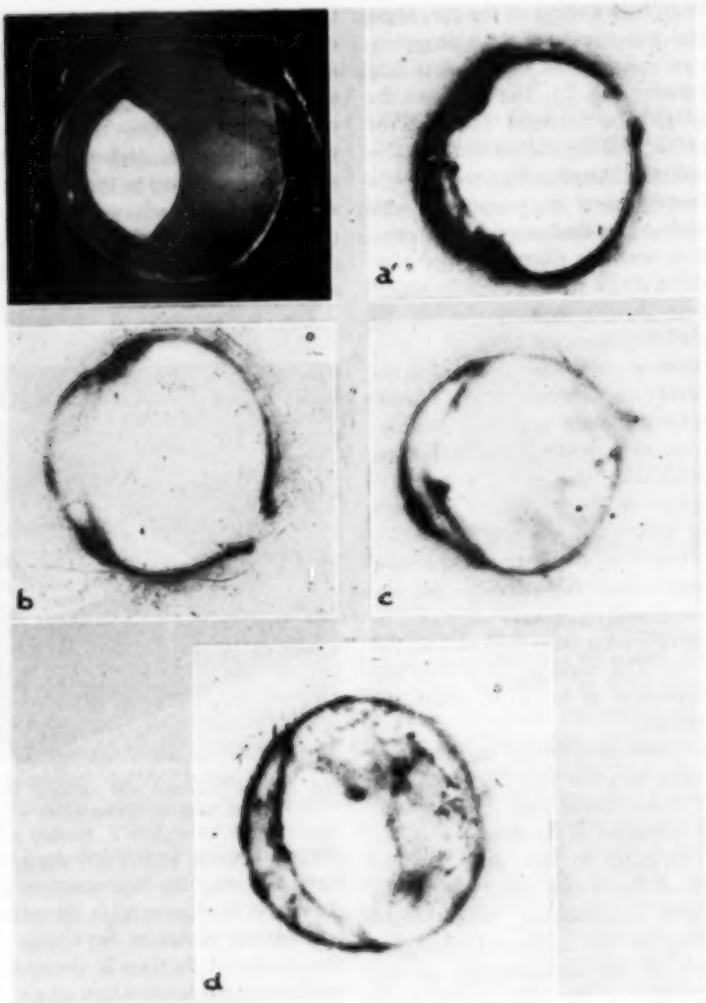


Fig. 3 (von Sallmann and Dillon). (a) Frozen eye slice. Radiographs of frozen slices of rabbit eyes at (b) one hour; (a') two hours; (c) six hours; (d) 24 hours, after intraperitoneal injection of radio-iodine (one microcurie).

ous space resulted obviously in a considerable increase of the radio-element in the aqueous humor one hour after intraperitoneal injection of the labeled compound. In these radiographs the outline of the cornea could not be differentiated from the region representing the anterior chamber. In eyes with intravitreal infections, slightly increased quantities of I^{131} were indicated in the radiographs in the area of the vitreous base (fig. 4).

Radiographic images from thin paraffin sections of normal eyes 24 hours after intraperitoneal injection of I^{131} were ob-

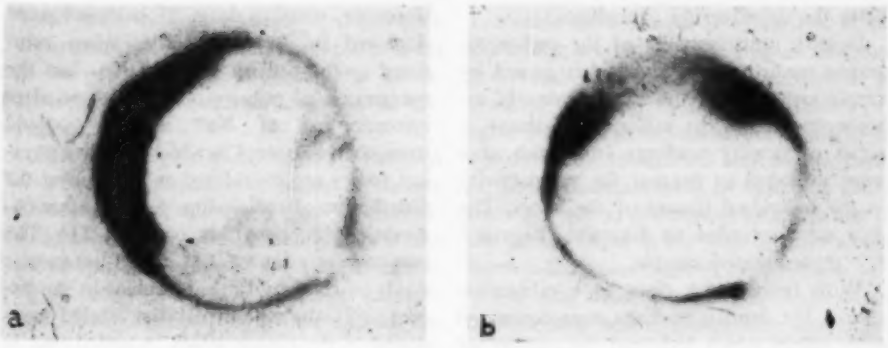
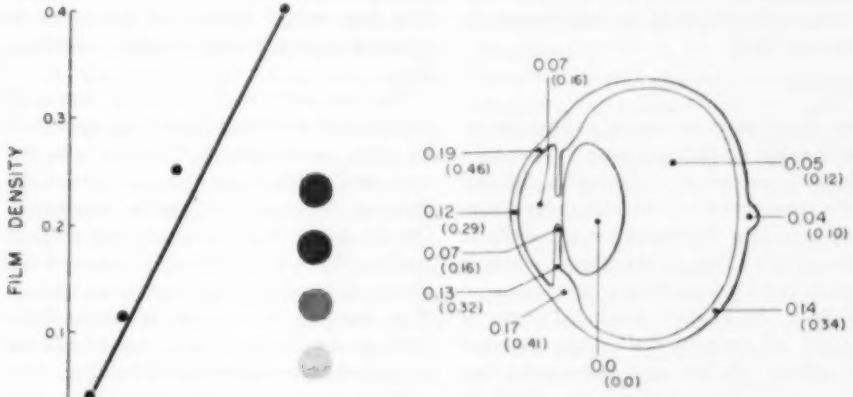


Fig. 4 (von Sallmann and Dillon). Radiographs of frozen eye slices from (a) rabbit with corneal ulcers and (b) rabbit with experimental endophthalmitis after intraperitoneal injection of I^{131} (one millicurie).

tained when fixation with alcohol or acetone was replaced by the dry-freezing technique and the sections were mounted on film without being floated on water. However, meager information was gained from these radiographs. Because of scattering effects, no critical localization of the source of radiation was possible in the radiographic image as far as membranes bordering on each other were concerned. It was not even possible to decide on the relative location of the labeled indicator in retina, choroid, or sclera, or in individual parts of the cornea. The second obstacle was the lack of histologic detail



A. Average densities of radiographs of agar discs containing I^{131}.

B. Radioactivity values (in parentheses) correlated with average densities in radiograph of frozen eye slice of rabbit one hour after intraperitoneal injection of I^{131}. (0.4 mc. per Kg. body wt.)

Fig. 5 (von Sallmann and Dillon). A sample of the diagrams upon which the data were recorded.

after the dry-freezing procedure.

Density measurements of the radioautographs confirmed the impression gained by simple inspection of the film. Because of inhomogeneities in the radiographic image, a series of density readings from each area were averaged to express the radioactivity in the individual tissues of the slices. The data were recorded on diagrams. Figure 5 is a representative sample.

With frozen agar discs as a calibration source, the density readings were correlated with values which indicated the amount of ionizing radiation that acted on the photographic emulsion. When the photographic densities of the discs were plotted as ordinates against their concentrations of I^{131} as abscissas, straight lines were obtained on which the radiation values of the radiographs of eyes could be interpolated. These are expressed in the diagram by the figures in parentheses. Discs made from agar solutions containing 0.05 to 1.0 microcuries per cc. produced on the film under standard conditions a scale of densities which covered the range of darkening in radiographs of frozen eye slices.

Comment

The distribution pattern of radioactive inorganic iodine in the eyes after systemic introduction, as seen in radiographs, differed greatly from that observed with radiosodium which is mainly confine to the extracellular space and from that of phosphorus which is characterized by intracellular penetration.

Wallace and Brodie[11] concluded from the similarity of experimental results obtained with iodine, chloride, and thiocyanate that iodides were distributed in the inorganic form throughout the body only in the extracellular fluid and that any chemical or physical relationship of iodides to tissue cells is improbable.

On the basis of examinations on a specialized organ, as the eye, no issue can be taken on the general problem of the distribution of iodides throughout the body. Moreover, massive doses of halogens were employed in previous studies when compared to the present investigation. But the comparison of radiographs of the eye after systemic use of Na^{24} and I^{131} would strengthen a concept in which selective physical forces are considered as influencing the distribution of radioiodine. Several other observations support this opinion: (1) The low concentration of I^{131} in the intraocular fluids as compared to the content in the tissues; (2) the amount of the labeled compound in the cornea which exceeded that in well-vascularized tissue in spite of the high concentration of the tracer in the blood; (3) the network pattern in the radiographs corresponding to the vitreous space and the demarcation line along the posterior surface of the lens indicating adsorption to phase boundaries.

In the old literature claims were made that tissues from tuberculous[12, 13] and streptococcal[14] intraocular infections, of testicular syphilis,[14] of experimental tumors,[15] or transudate and exudate[14] take up more iodine than normal tissues and that iodine in diseased tissue is present in organic combination.

The relatively high levels of iodide in exudate and pathologic tissue was confirmed by other investigators[16, 17] but it was felt that this distribution was not caused by chemical attraction or specific adsorption. On the basis of comparative experimental studies, Wallace and Brodie[17] proposed the theory that the greater concentration of iodine was due to increase of extracellular fluid present in the diseased organs and not to any inherent properties of iodides.

In the form given the hypothesis cannot be applied to explain the marked rise in concentration of the radiotracer in the aqueous humor and the moderate rise in the anterior part of the vitreous in inflammation. Here local hyperemia and a steep increase in capillary permeability for protein in the ciliary processes must result in augmented entrance of the labeled compound from the

blood with its high content of radioiodine. Its apparent accumulation in infiltrated areas in the cornea may be accounted for by increase of plasmoid extracellular fluid at this region.

The radiographs were instructive patterns since the topographic relationship of the eye tissues was not disturbed and the macrostructures were well defined. They illustrated the distribution of the labeled indicator in cornea, anterior chamber, anterior uvea, lens, vitreous, optic nerve, and the coats of the posterior segment of the eye, but did not permit localization of I^{131} in tissue constituents; nor was it possible to distinguish its concentration in retina, choroid, or sclera. These tissues together gave radiographically a single narrow line about one mm. in width.

The thin paraffin sections did not provide more accurate information. In historadiographs obtained 24 hours after systemic introduction of the tracer, the migration of the water-soluble compound by diffusion and partial loss in fixation seemed diminished by dry freezing, but accurate localization of the scattered reduced silver granules to details in the poorly preserved tissue was impossible.

The tortuous path of the photographically effective Beta particles, their straggling and scattering, obviated the purpose of the combination of histologic procedures and photographic techniques for thin sections of the eyes. Here optimal alignment of histologic details to radiographs of high resolution would be necessary for critical readings on adjacent membranous structures. It is for this reason that no attempts were made to apply microphotometry on such radioautographs although Axelrod and Hamilton had developed the technique.[4] However, frozen slices of the eye were adequate for estimating the densities of the film with a photometric device.

When obvious artefacts were avoided, average readings for cornea, aqueous humor, anterior uvea, lens, and posterior wall of the eye could be obtained. Irregularities in the darkening within the radiographic image of individual structures may be caused by residual blood in the vascular tissues—in spite of exsanguination of the animals—by adsorption of the labeled indicator to tissue or phase boundaries, or by technical shortcomings such as differences in apposition of the frozen slices to the film or unavoidable flaws in the smoothness of their surface.

The use of calibrated standards added another step in the quantitative evaluation of radiographs of the eye. The density readings could then be expressed in terms of radioactivity which had acted on the film. Studies on absorption and back-scattering of Beta radiations within the reference source have not been completed.

Comparison between densities of radiographs and radioactivity in the individual tissues of the eye

The purpose of this series of experiments was to determine whether the density measurements of radiographs signify true concentrations of I^{131} in the ocular tissues. Information on this question was obtained by comparing the radioactivities of tissues and fluids with densities of radioautographs of eyes from identically treated rabbits and in individual animals after systemic injection of radioiodine.

Technique. 1. For the determination of radioactivity in the tissues, the animals were killed by bleeding from the heart 24 hours after intraperitoneal injection of I^{131} (900 microcuries per Kg. body weight) and the globes were removed. The serum was saved and diluted 1:500 with distilled water. Aqueous humor was withdrawn in a 0.25 cc. tuberculin syringe and measured.

Cornea, anterior uvea, choroid, retina, sclera, optic nerve, and vitreous were separated and weighed. In six eyes, retina, choroid, and sclera were examined together and in eight instances they were separated. In seven experiments, corneal epithelium and

endothelium were scraped off and weighed on a semimicro balance which was also used for weighing retina, choroid, and optic nerve. The wet weights were recorded. Errors due to evaporation were reduced by keeping the sample in a moist chamber.

The tissues were finely minced in 1 cc. of distilled water. After 1 cc. of trichloroacetic acid was added the material was allowed to stand for one-half hour at room temperature. Then the samples were made up to 6 cc. with 10-percent sodium hydroxide. By stirring and warming the material three minutes in a boiling water bath, homogeneous tissue digests in alkali were obtained. The preliminary treatment with acid hastened the dissolving of the tissue. Five cc. of the digests and of the diluted serum were measured into flat tin pans (24 mm. diameter, 10 mm. depth) to serve as samples for examination in the G. M. counter (horizontal tank model). They were corrected for volume and background.

2. Possible loss of I^{131} which may have occurred during digestion of the tissue in heated alkali was examined in recovery experiments. Measured quantities of radioiodine were treated with five-percent trichloroacetic acid and 10-percent sodium hydroxide in the same proportion as used on the eye tissues. The mixtures were heated for three minutes in a boiling water bath. Counts made on these samples were compared with counts made on a control solution consisting of radioiodine in water.

3. Finally the possibility was considered that differences in self-absorption of Beta particles in the dilute tissue digests may have interfered with the results. A solution of radioiodine in distilled water, which contained one microcurie per cc. was prepared. One cc. of this solution or of distilled water was added to aliquot samples of tissue digests (4 cc.) for measurement in the G. M. counter.

Results

After adjustment to the radiation levels in serum, the results were reasonably consistent for the individual ocular tissues and fluids (table 1). Serum levels were low in 3 out of 9 experiments. The readings on radioactivity in tissues were of the same relative order as those determined by densitometry of radioautographs. Among the constituents of the eye, the cornea gave the highest relative counts although, in some instances, the sclera-choroid-retina readings were of about the same magnitude. However, they were lower than the serum values per weight unit. The latter were surpassed only by G. M. counts of corneal epithelium but evaporation of the small wet samples (4 mg. or less) during the process of weigh-

TABLE 1

RADIOACTIVITY MEASUREMENTS ON OCULAR TISSUES AND FLUIDS OF THE RABBIT 24 HOURS AFTER SYSTEMIC ADMINISTRATION OF I^{131} (0.9 MC. PER KG. BODY WT.) EXPRESSED IN PERCENTS OF SERUM LEVEL

Rabbit No.	Cornea	Anterior Uvea	Sclera	Optic Nerve	Vitreous	Aqueous
1*	65	40	65	23	14	35
2*	71	62	65	25	30	52
3*	62	50	40	25	23	52
4*	69	50	46	23	22	45
5*	67	47	49	41	16	34
6*	52	42	56	12	13	39
7	60	48	38	42	20	45
8	61	48	46	61	20	47
Average	64	48	51	32	20	44

* Eyes examined separately.

TABLE 2

COMPARISON OF DENSITOMETRIC AND RADIOMETRIC MEASUREMENTS IN 24-HOUR EXPERIMENTS WITH I^{131} WITH THE CORNEA TAKEN AS UNITY

	Cornea	Anterior Uvea	Sclera	Optic Nerve	Vitreous	Aqueous
Film Density (4 eyes)	1.0	0.8	0.7	0.6	0.5	0.7
G.M. Counts (14 eyes)	1.0	0.8	0.8	0.5	0.3	0.7

ing made the measuring of radiation for weight unit uncertain.

The G. M. counts per minute on isolated epithelium plus endothelium were in a range of 10 to 45. This increases the probable error of the results to about 15 percent. The same reservation in respect to accuracy must be applied to the relatively low readings on the optic nerve.

Taken together, isolated retina, choroid, and sclera had counts comparable to those of undissected inner and outer coats of the posterior segment. It could not be decided whether these adjacent tissues could be isolated without contamination with radioactive material from bordering structures. The overall agreement of G. M. readings with film densities is brought out in Table 2 where the number of counts and the degrees of density are expressed in fractions of corneal values.

The experiments of self-absorption of Beta rays in the samples and on loss of iodine in preparing the tissue digests in alkali gave uniform results. In the first group of tests the calculated values did not differ from the experimental values within limits of errors of the method as shown in Table 3. Even the greatest difference in chemical composition between individual tissue digests as, for instance, that of sclera and of vitreous did not indicate interference by self-absorption or back-scattering of the ionizing radiation in the liquid samples.

Heating of the tissue digests in alkali for three minutes (100°C.) did not bring about a measurable loss of iodine under the conditions and timing of the experiment.

COMMENT

Absorption of Beta particles varies with the chemical composition of the media through which they pass. Differences may occur within the heterogeneous tissues and fluids of the eye. Radioautographs would not express the actual distribution of the tracer if differences in self-absorption were present in thin slices. In this case the densities of the radiograph would be exaggerated in areas which correspond to parts of the eye with minimal content of solids. The G. M. measurements of the radiation in isolated ocular tissues and fluids gave evidence that such absorption was not of a magnitude that could be detected with the instruments and methods at hand.

For all practical purposes radiographs of frozen slices showed, therefore, the relative concentrations of I^{131} in various parts of the eye. Studies on self-absorption of Beta radiation in tissue digests and recovery experi-

TABLE 3

EXPERIMENTS ON DIFFERENTIAL SELF-ABSORPTION IN DIGESTS OF TISSUES AND FLUIDS OF THE EYE BASED ON G.M. COUNTER READINGS

		G.M. Counts per minute	Expected Counts per minute
Sclera	a.	788	790
	b.	672	669
	c.	560	555
Aqueous	a.	496	505
	b.	705	707
Vitreous	a.	784	771
	b.	896	890
Cornea	a.	562	560

ments of alkaline solutions of the radioactive indicator in heated samples gave support to the reliability of the G. M. measurements on isolated ocular tissues and fluids.

Nature of relative accumulation of I^{131} in the cornea

The problem of relative concentration of radioiodine in the cornea was approached by measuring in the G. M. counter the radiations in the acid soluble fraction and in the protein lipid residue obtained by treating the tissue with trichloroacetic acid.

Technique. The excised and wet weighed corneas were finely shredded in 1 cc. of distilled water. Proteins and lipids were precipitated with a 10-percent solution of trichloroacetic acid and separated from the supernatant acid-soluble fraction by centrifugation. The residue was washed twice in 10 cc. of the diluted acid. The washings were discarded. The supernatant of the first centrifugate which contained most of the acid-soluble compounds and the washed protein-lipid residue dissolved by adding two percent sodium hydroxide served as samples for determination in the G. M. counter. Four experiments were carried out two hours after the intraperitoneal injection of the radiotracer and five experiments after a lapse of 24 hours.

Results

No radioactivity in excess of background counts was recorded when the protein lipid fraction was examined two hours after administration of the indicator. The counts on the acid-soluble portion were in the range of those determined on cornea digests in alkali in the preceding series of experiments. In three instances (six eyes) very low readings were registered on the protein fraction at the 24-hour interval. In two instances the results were negative.

Comment

Since radioactivity could be demonstrated two hours after injection of the tracer exclusively in the acid-soluble part of the cornea, it was concluded that the radio-indicator was accumulated in the cornea as the inorganic salt. Twenty-four hours after injection the protein lipid residue seemed to have a small degree of radioactivity which was a minimal fraction of that determined in the supernatant. Assuming that the repeated washing had removed all traces of the acid-soluble part, the result would indicate that a small amount of radioiodine was organically bound at this time.

Radioiodine in the plasma is supposed to be protein bound to about 90 percent, 25 hours after systemic injection in rats with normal functioning thyroid glands.[18] It is probable, therefore, that the insignificant amount of organically bound iodine at the 24-hour interval has its origin in the protein-bound fraction of the plasma.

Summary

1. The distribution of iodine was studied in radiographs of eyes after local and systemic use of radioactive inorganic iodine (I^{131}).

2. The radioactive indicator was accumulated in the cornea and to a lesser degree in the anterior uvea after iontophoretic introduction from the cathode.

3. A relative accumulation of radioiodine in the cornea as compared to other parts of the eye was also observed at various time intervals after systemic use. Ocular tissues contained more of the tracer element than the ocular fluids. Infiltrated areas in the cornea seemed to trap more of the radioactive indicator than the rest of this tissue. In endophthalmitis the aqueous humor and —in a moderate way—the base of the vitreous produced increased darkening in the radiographs.

4. Radiographs of 10-micron sections of eyes were obtained 24 hours after systemic use of I^{131} but were not found useful for more accurate localization of the labeled compound in the tissues.

5. A technique of densitometric evaluation

of radiographs for frozen slices of the eye was designed. The density readings could be expressed in terms of radioactivity by using as reference standards agar discs containing measured concentrations of the radioactive indicator.

6. Densities of radiographic images were compared with the G. M. measurements of radiations in individual tissues or fluids of the eye under controlled conditions. Agreement between the results of both methods indicated that radiographs obtained with the use of I^{131} expressed the true quantitative distribution of the labeled compound in frozen slices of the eye.

7. Almost all of the radioiodine in the cornea is extracted in the acid-soluble fraction. A minimal amount of iodine could be determined in the protein-lipid residue 24 hours after injection of the radiotracer.

We are greatly indebted to Dr. Z. Dische, biochemist, of the Department of Ophthalmology, for valuable suggestions in planning and executing the experiments in several phases of the study. Our thanks are due to Dr. G. Failla and Dr. E. H. Quimby, Department of Radiological Research, for expert advice and permission to make use of the tracer supply and the laboratory equipment of the department; to Miss C. Schmidt of the same department for constant coöperation; and to Miss P. Pfaff, Department of Ophthalmology, for help in the experiments on histologic procedures.

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Discussion

Dr. Henry Minsky (New York): From a purely anatomic point of view, Dr. von Sallmann's demonstration in these pictures tends to prove to me that the relatively dense shadows thrown by the so-called "base of the vitreous" are really those of the zonular fibers originating from the ciliary epithelium of the pars plana. It is a real tissue and should be considered a part of the aqueous system. The "base of the vitreous" itself is distinctly different from the body of the vitreous, and should be considered as an extension of the ciliary epithelium since it is the source of these zonular fibers (hyalo-zonular leaf) running on the face of the vitreous and in the hyaloid all the way to the posterior surface of the lens.

Dr. Frank Vesey (New York): I wonder if Dr. von Sallmann thinks that the density of the ciliary body would mean that the radioactive material is carried away from the inside of the eyeball through that route?

To my mind, and of course we are all looking for things that will prove our own thinking and theories, it would prove that the channel of outflow is definitely not Schlemm's canal, because I have not seen a single picture in which Schlemm's canal area was in any way more expressed than the rest of the eye.

In fact, it was less expressed on those photographs. I would be inclined to think that the route of outflow is definitely shown to be the ciliary body, especially the ciliary processes, and the iris. That again would mean that the whole theory of glaucoma, based on the single conception of mechanical means—that is, that once the chamber angle is obstructed then glaucoma ensues—is untenable.

Dr. Ludwig von Sallmann (New York): It is not possible to identify in macroradiographs histologic structures of the size of Schlemm's canal and to judge the amount of tracer material accumulated there.

A SLING RETRACTION SUTURE FOR THE UPPER LID DURING CATARACT SURGERY

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Since the advent of modern cataract surgery, the escape of the vitreous humor through the lips of the corneoscleral incision has been an accident feared and guarded against by all operators. Because this complication rarely or never occurs in the presence of normal vitreous if no external pressure is applied to the globe, numerous ingenious means have been devised to relieve the eyeball of all positive external pressure. The large number of eyelid retractors and self-retaining speculums and their modifications are proof of the unsatisfactory nature of most of them.[1] Stevenson,[2] in 1916, stated that it would be better if, in all cataract operations, the eye speculums were discarded during the entire procedure.

F. E. and E. P. Burch[3] list the two most frequent complications of cataract surgery as loss of vitreous during the operation and postoperative prolapse of iris. Loss of vitreous may be due to several factors, including an apprehensive patient and a nervous operator, but squeezing of the lids when the orbicularis is not paralyzed, or pressure from an eye speculum, or from a partially everted upper eyelid, which causes the upper part of the tarsal plate to press into the globe, are the most frequent causes. Orbicularis spasm is adequately controlled by proper and complete anesthesia and akinesia; pressure from the eyelids must be avoided through the use of mechanical means, whether with (a) the fingers of an assistant, (b) the use of a metal "blepharostat," or (c) by the employment of sutures into or through the eyelids to raise them from the globe.

RETRACTION WITH FINGERS

The use of the fingers for retraction of the eyelids was undoubtedly the first means employed and has been advocated even in comparatively recent times. Vail,[4] in 1916, said that with a coöperative patient, the only thing required is retraction with the fingers. Much of Colonel Smith's success in India he felt to be due to the skillful help of Nur Ali, his Mohammedan assistant, in controlling the eyelids with finger manipulation. In 1927, Edeskuty[5] noted that, when working with unruly and uncoöperative patients and with untrained assistants in Colombia, he preferred the use of lid sutures but that, when he had good help and a cooperative patient, he would choose the fingers of his assistant for retraction of the lids. In 1911, Hulen[6] advised control of the lower lid by the thumb of the assistant, and Ohm,[7] while advocating the use of sutures for the upper lid, felt that adequate control of the lower lid was maintained by the index finger of the assistant.

RETRACTION WITH BLEPHAROSTAT

The lid speculum with its many modifications (Knapp, Murdock, Weeks, Berens, Beard, Wiener, and so forth) is familiar to every ophthalmic surgeon, as are the various types of retractors—the Desmarres, Green, Fisher, and so on. Horner[8] states that, of 15 such instruments in a surgical supply catalogue, none was found to keep pressure entirely off the globe. However, numerous ingenious devices to accomplish this function are found in the literature, none

of which has proved to be the ultimate answer to the problem.

In 1915, Brownfield,[9] feeling that the ordinary eye speculum served well enough to separate the eyelids but in no wise prevented pressure on the eye, devised an instrument combining the principles of a retractor and an elevator, the two features being independently adjustable. The retracting or separating arms are of the usual type, and their position in the anteroposterior axis depends on the action of a set-screw which, when tightened, causes the elevating arms to bear on the upper and lower orbital rims, thus raising the lids off the globe to any height desired.

In the following year, two articles appeared concerning the management of this problem. Vail[4] advised that, because the reflected arms of the average speculum do not reach far enough up on the tarsus, which may buckle with orbicularis spasm, in such an event, lifting the speculum will allow the lids to slip out.

Vail advocated the use of two special retractors, one larger for the upper lid and one smaller for the lower lid. These retractors are made of hardened steel, with a single bar on which hangs the tarsus. On the end of this bar is a cross bar, curved to suit the contour of the globe, and to hold the loose tissues of the fornices. A heart-shaped plate near the head keeps the cilia out of the way, and the handle is short, flat, and corrugated for better grasping.

Because of the tendency for the corrugator supercilii and the muscles of the cheek and side of the nose to act synergistically with the orbicularis in producing dangerous spasm, he advised finger traction by the assistant up on the brow and down on the cheek so as to involve all muscles in the retraction.

Stevenson[3] advised discarding the eye speculum in favor of Dr. Fisher's fenestrated upper-lid retractor in conjunction with his lower-lid hook. The handles of the retractors were to be elevated only during the actual expression of the lens, so as to draw the lids upward and out of the orbit.

An elaborate apparatus was designed by Crossley,[10] in 1917, absolutely to immobilize the patient's head, as well as the eyelids. This consists of two parts: a base with a pad for the patient's occiput and two metal uprights with attached pads for the sides of the head; to the uprights is attached the superstructure, a metallic frame with cross-bars on which are mounted two sliding locks to fix the two lid hooks or retractors. The entire device is locked to the operating table.

Another rather elaborate device was propounded by Cullom,[11] in 1932, in an attempt to get the speculum off the eye so as to prevent loss of vitreous. This method employs a metal head-band, a smaller band around the back of the neck, and a vertical bar between the two to which is attached an eye speculum that can be adjusted both vertically and horizontally.

Castroviejo's mosquito lid-clamp retractors[12] were originally designed for patients who could not retain an ordinary speculum because of symblepharon formation, as from trauma, burns, trachoma, and so on. But they are also recommended in cataract extraction to avoid pressure on the globe. These retractors are essentially small metal clamps in the shape of the letter "U," 5 mm. long by 3 mm. wide, with the eyelid inserted into the space between the arms of the "U" and held in place by a thumb-screw, somewhat like an earring. A suture is passed through an eyelet in the flange to exert traction, and the suture is fastened to the head-drape by means of a hemostat. Four of these retractors are suggested in cataract surgery, two on the upper lid, one on the lower, and one at the outer canthus, which latter may obviate the need for canthotomy.

In a paper entitled "Lid traction the greatest safeguard against vitreous loss in cataract operations," Obarrio[13] considered the ocular cul-de-sac as the walls of a piston closed proximally by the globe. Thus, when

the lids are lifted, negative pressure is produced in this pistonlike arrangement, and the cornea will be depressed. He advocates the use of a speculum, to be lifted up the moment the globe is incised, and this traction to be maintained until the dressing is applied at the completion of the operation.

With this same idea in mind, Professor Elschnig[14] recommended, in addition to a Desmarres retractor, the placing of four sutures, one through the tendon of each rectus muscle, with retraction to be made at an angle of 30 degrees from the sagittal plane on each suture. This, he felt, produces a minimum of pressure—even a negative pressure in the globe—and minimizes the tendency to loss of vitreous.

Quite recently, Hylkema[15] has recommended an eye speculum with a different type of blade for the two lids. Because the upper and lower eyelids differ considerably in form and in their relation to the surrounding tissues (the upper tarsus being broader, and connected with the levator), so that the lower lid is much easier to pull down and off the globe, he recommends a speculum whose upper blade is bent in the shape of a saddle and, in addition, is arched parallel to the surface of the eyeball. This blade rests snugly, well back on the under surface of the superior orbital rim. The blade for the lower lid is shorter and curved, very similar to the tip of a Desmarres retractor. To avoid any pressure from the upper blade on the eyeball, it is provided with a small curved piece of wire, or eyelet, through which a thread can be passed and pulled up by an assistant if necessary. The blades of this instrument are interchangeable, for use with either eye, and the hinge of the instrument has an adjustment screw resting on the patient's temple by which the speculum can be tilted slightly to improve the adaption of the blades to the eyelids.

Retraction with sutures

Because these speculums and their modifications have not proved entirely satisfactory in relieving the opened eyeball of all pressure, considerable thought has been given to the employment of the third form of retraction—that is, the use of sutures through the eyelids. The usual method of placing these sutures is described by McCool.[16] Three double sutures of No. 3 white twisted silk are inserted three mm. from and parallel to the upper lid margin to include the skin, muscle, and pretarsal fascia, and, if possible, a portion of the tarsal plate. One suture is placed in the middle of the lid, one midway between it and the external canthus, one midway between it and the internal canthus, and the silk threads are held parallel by a forceps, the two central ones being drawn up shorter to insure a curved lid border. He feels that if only one central suture is used, the sides of the lid margins may compress the globe due to the V-shape produced. Using this formula as a basis, many deviations of lid retraction sutures have been suggested.

Jacqueau,[17] in 1927, advised the injection of novocain followed by the insertion of a silk thread right through the upper tarsus so that the thread comes out, not on top of the lid, but on the free edge. In the same year, Edeskuty's paper[8] appeared, recommending the use of a long silk suture through the skin of the upper and lower lid margins, as well as a superior rectus bridle suture, whenever one had to deal with an uncoöperative patient, or the assistant was not adequately trained.

At about this time, Warschawski,[18] advocating the use of the superior rectus bridle suture for elevating the lids as well as rotating the globe downward, stated that this method gave better exposure and avoided the use of fingers.

Elaborating on this theme, Gill,[19] in a relatively recent paper, does not use a speculum, the lids being held open and the eye rotated down by silk sutures. The upper suture is placed under the superior rectus muscle, 4 to 6 mm. back of its insertion, and the lower lid is held down by a suture

placed through the skin near the lid margin, both sutures being attached to the drapes by hemostats. The advantages claimed for this method are the elimination of pressure at the globe, minimizing the possibility of vitreous loss; the operator is put at ease, which is conducive to better results; and the eye can be closed quickly if necessary.

O'Connor,[22] in 1934, advocated upper lid sutures. The two sutures he used were placed in the middle of each half of the upper lid, just above the lash line. They included the skin only. The ends, arranged to give an even lift, were grasped by a hemostat which was then dropped over the top of the head.

Horner,[8] in 1935, recommended the use of lid sutures to aid the surgeon who operates with an untrained assistant. He used white silk, two mm. from the lid margin and parallel to it, one in the lower lid and two in the upper. In the upper lid, each suture was placed three mm. from the midline, and emerged eight mm. away—thus a space of six mm. separated the central portions of the sutures.

The four strands were spread and caught with a hemostat after adjusting to equal tension on all four, and the clamp was held by an assistant so that the lid could be moved over the globe or to the right or left readily.

The same author subsequently[20] recommended a modified hemostat with closely fitting jaws which would hold throughout its entire grasping surface the four silk threads in the upper lid. Thus, the "tenting" of the lid which occurs if the threads are held at a common point could be avoided. The upper blade of this clamp bears a small hook to which may be fastened the superior rectus suture, if one is used.

Paton and Abbott,[21] disturbed by the tendency for lid retraction and superior rectus sutures to shift position due to slipping of the drape-sheet to which they are anchored, devised an apparatus to avoid this possibility. This consists of a woven headband, to which are attached two 2 by 1½ inch aluminum plates, one above each eye. Attached to each plate is an elevated metal strip, 3/16 inch high and 9/16 inch wide, in the form of a "T," tapered at the edges to facilitate the clamping of hemostats to either side. The lid sutures are secured to the upper border of the "T" through the drapes, and a firmly rolled cotton sponge is placed under the suture just above the level of the brow.

Roberts[1] describes a method designed to do away with the use of a speculum which is quite similar to that propounded by Edeskuty.[5] A stitch is inserted into the skin of the upper lid near the lashes and opposite the 12-o'clock position in the cornea. The upper lid is drawn up by traction on this suture and held in position by mosquito forceps anchoring it to the towels around the head at the level of the upper forehead; the lower lid is retracted downward by a bent wire retractor held by an assistant, exposing the eye without pressure.

The eyelid retraction suture which most closely approximates the one to be advocated in this paper was suggested by Ohm,[7] in 1927. He gives credit to Liebermann for first mentioning, in 1918, the use of lid sutures for fixation and eversion of the lids in operations on the thickened tarsus and conjunctiva in trachoma. Ohm found that upper-lid sutures were very satisfactory in cataract surgery, and his method very nearly obviates what has seemed to us to be the great disadvantage of placing the sutures at or near the margin of the upper lid—namely, the tendency for the lid to evert partially or wholly, and thus exert pressure on the upper portion of the sclera through the medium of the firm tarsal plate. Ohm uses three sutures above, two of these being through the skin of the lid margin at the inner and at the outer one-third. The third suture is centrally placed, but five mm. higher in the middle of the upper lid. He states that this difference in the placement of the central suture keeps the upper lid from turning inside out, and thus prevents pressure on the globe.

Neither of us has been entirely satisfied with any of the above methods for retracting the upper lid in cataract surgery. Each of us, acting as assistant and using sutures placed at the margin of the upper lid, has caused loss of vitreous when the upper margin of the tarsus of the partially everted lid produced pressure on the globe as the cataract was being delivered or just after it was delivered.

Not knowing of Ohm's[7] method of using sutures in the upper lid we tried a very similar suture. We placed the upper central suture just above the tarsus in the levator tendon. This made partial eversion of the lid less likely but did not give as good control over the lid as the method we shall describe next—a method we have employed on approximately 40 cataract extractions with entirely satisfactory results.

The sling suture

The lid-retraction sutures which we use are size-A cotton, thyroid, or general surgical thread. They are blue in color to distinguish them from the black-silk superior rectus and corneoscleral sutures to be used subsequently. After Van Lint akinesia supplemented by local infiltration of two-percent novocain into the skin and subcutaneous tissues of the upper lid, and margin of the lower lid, the lid sutures are placed.

Three 3/8-circle surgical needles with cutting edge (#1848-1, Anchor Brand) are threaded with about 10 inches of the blue, size-A suture, and the upper lid is everted in the usual manner to expose the palpebral conjunctiva. The needle point is now inserted into the conjunctiva just superior to the upper margin of the tarsal plate at the junction of the inner and middle thirds of the eyelid. Care must be taken that no portion of the bulbar conjunctiva is inadvertently picked up on the needle point as it is started through the lid.

The eyelid is now returned to its normal position and the needle is brought out through the levator tendon, orbital septum, orbicularis, subcutaneous connective tissue, and the skin. The thread is now pulled through the eyelid until an equal length emerges from the skin and from below the lid margin. A second suture is similarly placed at the junction of the middle and outer thirds of the upper eyelid.

The four strands of suture are now tied together about 3 or 4 inches from the lid and tarsus (fig. 1), which can be freely

Fig. 1 (Quinn and Stansbury). Sling retraction suture in the upper lid of the left eye, holding the lid completely away from the eye.

manipulated by the fingers of the assistant. Or, if preferred, the four strands may be grasped with a hemostat after they have been pulled up so that the tension is equal on all four (fig. 2). There is no fixation of the sutures to the free margin of the lid so that they can be moved medially or laterally at the margin to obtain the proper contour of the lid and prevent side pressure of the lid on the globe.

Canthotomy is done if there is the slightest need for it, and is a great aid in relaxing an anatomically short upper lid, making it easier to control.

The lower lid usually does not present a problem so the suture is placed through the skin and subcutaneous tissues close to

and parallel to the lid margin in the middle third. However, a sling suture may be used in the lower lid if desired.

We feel the sling suture for the upper lid has all the advantages of any suture, prevents pressure of a partially everted tarsus on the globe, and gives much better control over the lid. It is much safer in the hands of an untrained assistant than is a retractor.

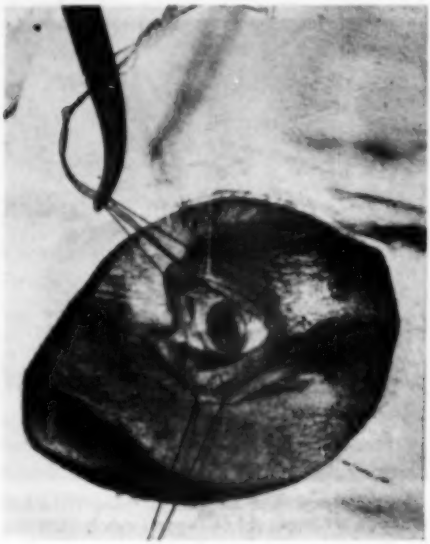

Fig. 2 (Quinn and Stansbury). Sling retraction suture controlled with a hemostat.

It may be entrusted to an intern or a nurse when there is a shortage of trained assistants. The tarsus is not traumatized, since the needle and suture do not pass into it as advocated by some authors.[16,17] A superior rectus bridle suture may be used if desired and can be controlled by another finger of the hand which controls the sling suture. If the assistant's hand is in the way of the operator, a firm cotton roll may be placed over the brow and the sutures carried over the pledget. Traction is made in a line parallel to the forehead, which serves to pull the lid forward as well as upward.

At the end of the operation and before the sling suture is removed, a silk or cotton suture is placed through the skin and subcutaneous tissue near and parallel to the margin of the upper lid in the central one third. The sling sutures are now removed by gentle traction after each has been cut at its point of emergence through the skin. With the aid of the marginal suture, the lid is now lifted over the wound without danger of catching in it. The marginal suture is then fastened to the cheek with adhesive plaster until orbicularis function returns. Van Lint akinesia is preferred because adequate akinesia, as well as local infiltration of both eyelids, can be obtained with one introduction of a needle four cm. long.

Castroviejo[12] cites two disadvantages in the use of eyelid retraction sutures. The first of these—pain—is readily abolished by the proper use of cocaine instilled into the cul-de-sac and by local infiltration with procaine. The second—hematoma, which increases the risk of infection and produces temporary disfigurement—has not been encountered in our experience, but its possibility must be acknowledged.

Summary and Conclusions

The literature concerning cataract extraction is replete with ingenious methods for avoiding positive pressure on the opened eyeball. The very multiplicity of devices designed for this purpose is an indication that none is entirely satisfactory. Three general types of eyelid retraction are available: (1) Fingers of the assistant—a method not much in vogue today; (2) employment of a metal "blepharostat," whether in the form of a speculum or a retractor; and (3) the use of sutures for raising the eyelids from the globe.

Since no blepharostat was entirely adequate in our hands, various types of lid sutures were used and a method was devised which seems most satisfactory in overcoming the various objections to the other methods. This consists of two sling sutures which pass through the entire thick-

ness of the upper eyelid, just above the tarsal plate, and are tied or fastened together to form a sling or hammock for the support and manipulation of the eyelid.

The advantages of this method are believed to be: (1) It prevents pressure on the globe from a partially everted tarsus and consequent loss of vitreous, but does not traumatize the tarsal plate; (2) only one hand is required to manipulate this suture and a superior rectus bridle suture, if used; (3) the lid can be lifted off the opened eyeball, moved from side to side, and the eye can be closed quickly; (4) the sutures can be arranged to give the upper eyelid the proper contour and avoid undesirable compression of the globe from the sides of the lid; (5) no instrument is present that requires removal when it is necessary to close the lids quickly or at the completion of the operation; (6) this suture is safer than a retractor in the hand of an inexperienced assistant.

Experience with this type of eyelid retraction in a relatively small series has been quite satisfactory and the method is felt to be a worthwhile adjunct to the technique of cataract extraction. It effectively mediates against the loss of vitreous humor through unwarranted pressure on the globe.

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ACUTE GLAUCOMA INDUCED BY HOMATROPINE

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As early as 1867 Derby[1] described two cases of acute glaucoma directly following the instillation of atropine for routine examination. Green,[2] in 1880, described a case of acute glaucoma secondary to duboisine application.

In 1885, Hodges[3] described the first recorded attack of acute glaucoma following the use of homatropine instilled for the purpose of refraction. The symptoms of bilateral ocular pain, nausea, and vomiting supervened 26 hours after instillation. Tension to fingers prior to the homatropine instillation had been normal. Two days after treatment with eserine drops the ocular tension was again normal. Three weeks afterward the corrected vision was again normal and the field examination showed full findings.

In 1902, Standish[4] reported 32 cases of glaucoma before the New England Ophthalmological Society in which nine were precipitated by atropine, two by homatropine, one by cocaine, one by scopolamine, and one case by duboisine.

Ring,[5] in 1903, reported a case of acute glaucoma following a drop of euphthalmine instilled for diagnostic purposes. Prior to instillation in this case confrontation field examination was done and tension to fingers was taken in each eye and found to be normal. There was, however, a positive history of intermittent attacks of dim vision. It was necessary to perform an iridectomy to control the pressure permanently in this case.

Sutphen,[6] in 1916, described a case of bilateral, acute glaucoma precipitated by atropine in a 38-year-old patient. Surgical procedures were necessary on each eye to maintain tension within normal limits.

More recently, in 1941, postmydriatic glaucoma was given careful study by Beach and Holt[7] who reported nine cases, five of which were secondary to the use of homatropine. In two of the nine cases it was necessary to resort to surgery.

Since the use of homatropine as a cycloplegic in adults still is almost universally accepted, the following cases of severe acute glaucoma precipitated by it are presented.

CASE REPORTS

CASE 1

History. Mrs. M. D., a widow, aged 66 years, reported to my office on October 14, 1947, with a complaint of not being comfortable with her present glasses. Her last refraction had been five weeks previously. The glasses she was wearing were: O.D., +1.25D. sph.; O.S., +1.75D. sph., with a near addition of +1.25D. in each eye.

Ocular examination revealed vision to be: R.E., 20/200; L.E., 17/200. The external examination was normal; this included a gross check of pupillary action to light and accommodation and a gross inspection of the anterior chamber. The nerveheads were normal. The tension to fingers in each eye was normal. The peripheral form fields taken with a one-degree test object were full and the central fields taken with a 0.5-degree form test object on the stereocampimeter showed normal blindspots with no scotomas.

One drop of one-percent homatropine was instilled in each eye. One hour later the patient was refracted with the following findings: O.D., +2.5D. sph. $\bigcirc$ −1.25D. cyl. ax. 90° = 20/20; O.S., +3.5D. sph. $\bigcirc$ −1.5D. cyl. ax. 80° = 20/20. The pupils dilated round and equal to 5 mm. The ocular fundi were normal except for a moderate amount of sclerosis of the retinal arterioles.

The next day the patient reported to the office with severe pain in the right eye, nausea, and vomiting. Examination revealed an acutely chemotic right eye with a cloudy, shallow anterior chamber and a tension of

75 mm. Hg. (Schiøtz) in the right eye, and 27 mm. Hg in the left eye.

Slitlamp examination showed much bedewing of the right cornea with no visible keratic precipitates. Slitlamp examination of the left eye revealed normal findings. The patient was given 0.25-percent eserine drops to use every hour in the right eye during the day and every two hours at night. Tension the following day was 23 mm. Hg (Schiøtz) in each eye. The patient was then instructed to use the drops four times daily in the right eye.

On October 20th, six days later, the Schiøtz tension was: R.E., 45 mm. Hg; L.E., 23 mm. Hg. The eserine was then increased to six times daily. Slitlamp examination at this time showed some old pigment deposits on Descemet's membrane and a moderate amount of iris atrophy. From this date until November 25, 1947, the tension varied from 32 to 48 mm. Hg (Schiøtz) in the right eye.

Operation. The patient was hospitalized on November 30, 1947, at which time a corneoscleral trephination was done without complication. Since that time, the tension in each eye has not been over 25 mm. Hg (Schiøtz). Peripheral and central form fields remained full. On November 9, 1948, the last date the patient was seen, there was some posterior cortical lens opacity in the operated eye which reduced the corrected vision to 20/50. The left eye has remained normal.

CASE 2

History. Mrs. W. H., a housewife, aged 53 years, was first seen as a private patient on March 31, 1941, for a routine refraction. Tension to fingers was normal, peripheral form fields were full, and corrected vision under the use of homatropine (one percent) in each eye was 20/20. On two later visits this same examination was repeated with similar findings.

This patient reported for her fourth routine refraction on July 15, 1948. There were no complaints on this visit, the patient only desiring a recheck of glasses which had been prescribed on April 4, 1946. There had been no episode of dim vision or rings around lights.

Ocular examination revealed vision to be 15/200 in each eye. Gross reaction of the pupils to light and accommodation was normal. Tension to fingers was normal. On loupe examination, the depth of the anterior chamber appeared within normal limits. The nerveheads were normal. The peripheral form fields with a one-degree form test object were full. The central form fields with a 0.5-degree form test object showed a normal blindspot in each eye with no scotomas.

One drop of one-percent homatropine was instilled into each eye at 10 a.m. One hour later refraction revealed: O.D., +2.5D. sph. ⌒ −0.5D. cyl. ax. 120° = 20/20; O.S., +2.25D. sph. ⌒ −0.5D. cyl. ax. 60° = 20/20. This was only a slight change from previous refractions. The ophthalmoscopic examination showed normal findings with no evidence noted of corneal edema.

At 10 p.m. the next day the patient's husband, who had had chronic glaucoma for three years himself, called stating that the vision in his wife's right eye was hazy, similar to the haziness he experienced at intervals. The patient was having a feeling of fullness but no severe ocular pain. The husband was instructed to put a drop of his two-percent pilocarpine in his wife's right eye twice before she retired at 11:30 p.m. The patient was seen in the office the following morning at which time the Schiøtz tension was: R.E., 45 mm. Hg; L.E., 22 mm. Hg.

Slitlamp examination showed much bedewing of the right cornea, no keratic precipitates, a definitely narrowed chamber angle in the right eye, and a suggestion of narrowing in the left eye. A prescription for 0.5-percent eserine was given to the patient with instructions to use it every two hours in the right eye until retiring at midnight then to continue again at 7 a.m.

Course. Tension the following day was: R.E., 50 mm. Hg (Schiøtz); so the patient was hospitalized. The 0.5-percent eserine was continued day and night. Dehydration was attempted with 0.5 cc. of salyrgan intravenously every second day, and 50 cc. of 50-percent glucose were given intravenously three times daily. At the end of two days, a paracentesis was done on the involved eye under pentothal anesthesia.

Since there was no improvement at the end of five days of hospitalization, a corneoscleral trephination was done on August 22, 1948. While the patient was hospitalized repeated tension readings over several 24-hour periods showed no tension elevation in the left eye above 25 mm. Hg (Schiøtz).

On December 9, 1948, the peripheral and central form fields were full in each eye. At that time the patient was using atropine (0.5 percent) ointment in the right eye once daily. There was a good filtering bleb. Slitlamp examination revealed a few fine pigment deposits on the posterior corneal surface, moderate iris atrophy; and a clear lens in the right eye. Vision in each eye was correctible to 20/20, and tension in each eye was under 25 mm. Hg (Schiøtz).

CASE 3

History. Mr. J. P., a school teacher, aged 63 years, was first seen as a private patient on February 1, 1947. History revealed tearing in the right eye for a period of four months. The patient stated that there had been no vision in the left eye for 13 years. The cause of the visual loss in this eye was attributed to "a scar on the eyeball." For three years the patient had been using a drop of medicine in the right eye before retiring. No oculist had been consulted for three years and the reason for using the drops was unknown to the patient.

Ocular examination revealed vision in the right eye of 20/200 correctible, with the patient's glasses, to 20/25. There was no light perception in the left eye. The pupils were quite small and reacted poorly to light. The Schiøtz tension was: R.E., 23 mm. Hg; L.E., 27 mm. Hg.

Slitlamp examination revealed a superficial corneal scar in the right eye, a slight amount of iris atrophy in the right eye, and a moderate amount of iris atrophy in the left eye. The chamber angle in the right eye was slightly narrowed and definitely narrowed in the left eye. It was impossible by ophthalmoscopic examination to see the nerveheads. The peripheral form field taken with a one-degree test object was essentially full; central form field with a one-degree test object showed slight enlargement of the normal blind spot.

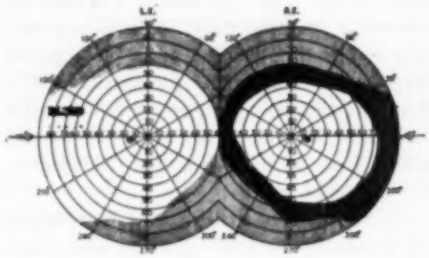

Fig. 1 (Linhart). *Case 3.* Peripheral form field of right eye taken on the perimeter with a one-degree test object prior to instillation of homatropine. The left eye was blind.

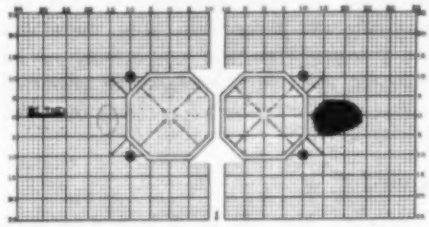

Fig. 2 (Linhart). *Case 3.* Central form field of right eye taken on the stereocampimeter with a one-degree test object prior to instillation of homatropine. The left eye was blind.

One drop of 0.5-percent homatropine was instilled into each eye. One hour later refraction revealed; O.D., +3.0D. sph. ⊂ −0.75D. cyl. ax. 62° = 20/20.

The ophthalmoscopic examination showed moderately deep, glaucomatouslike, nerve-

head cupping in the right eye and extensive cupping with advanced atrophy in the left eye. The Schiøtz tension was: R.E., 41 mm. Hg; L.E., 56 mm. Hg. Several drops of 0.5-percent eserine were instilled at 20-minute intervals into each eye. The patient was then sent home with 0.125-percent eserine drops with instructions to use them every two hours continuously in each eye.

The following day the patient complained of moderate pain and considerable fogginess of vision. Tension was: R. E., 56 mm. Hg (Schiøtz); L. E., 48 mm. Hg. The patient was then given a prescription for one-third percent eserine and instructed to use it five times daily in each eye. Twenty-four hours later, tension was: R. E., 11 mm. Hg (Schiøtz); L. E., 20 mm. Hg. The patient was put on pilocarpine (one percent) three times daily; this was continued until the patient was last seen on November 29, 1948. The Schiøtz tension had been maintained at 26 mm. Hg or below that figure in the right eye but had ranged up to 45 mm. Hg in the left eye. There had been no further field loss in the right eye and the corrected vision had remained 20/20.

Comment

The sudden onset and severity of these cases of acute glaucoma following administration of a known initiating drug would seem to indicate that there were predisposing factors present in these eyes. There is a deficiency of cholinergic substance in the aqueous of glaucomatous eyes with a vasomotor irritability which may act as a trigger mechanism.[8] This concept of a threshold, with the trigger mechanism being set off by a cycloplegic, seems to fit these cases. Gradle[9] has shown that, in 2.8 percent of 500 eyes studied, there was an increase of 5 mm. Hg or more in the intraocular pressure following the use of a cycloplegic for refraction.

It is quite likely that in the first two cases we are dealing with a mild form of glaucoma, without visual form-field or nervehead changes, which may have only transiently elevated intraocular pressure. In some cases of glaucoma the disease may be so mild that the fundus, fields, and central vision remain unaltered for years. In 373 cases studied by Posner and Schlossman,[10] 40 had the mild form.

On loupe examination of the involved eyes in the first two cases the chamber angles could be considered as normal. Slitlamp examination of the third case proved it to be definitely of the narrow-angle type. The shallow-angle cases, as a rule, show the greatest tension rise on administration of a cycloplegic. Kronfeld and co-workers[11] studied the effects of mydriasis in patients with wide-angle glaucoma and came to the conclusion that the intraocular pressure was not grossly influenced by the administration of mydriatics.

Stine[12] studied 82 eyes which were subjected to mydriasis, of these 33 were of the wide-angle type; 18, narrow-angle; and 31, normal. In his series, the rise in pressure in the wide-angle type was less than 1 mm. Hg, while the mean rise in the narrow-angle type was 14.3 mm. Hg.

In view of the importance of the chamber angle in the production of cycloplegic glaucoma, gonioscopic studies can be of extreme importance. So-called preglaucomatous eyes or normal eyes can be watched for further evidences of impending glaucoma as suggested by Gradle and Sugar.[13] Unfortunately no gonioscopic studies of the chamber angle were done in these cases. Slitlamp examination gave a rough idea of the condition of the chamber angles.

There is no doubt that, in all of these cases the nature of the glaucoma was permanently altered after homatropine administrations. This was even true in the third case which was controlled medically.

Treatment

Most ophthalmologists are agreed that surgery must be performed only as a last resort in these cases. Miotics will almost invariably terminate the attacks. In the nine cases of

Beach and Holt,[7] two required surgery; one of these had a corneoscleral trephination, while another, a bilateral case, had iridectomies. Sutphen,[6] in his bilateral case initiated with atropine, did a paracentesis of each eye followed by iridectomies. His complication of prolapsed uveal tissue at the site of the incision prompted his suggestion that future cases should have a filtering operation such as the Lagrange.

The two surgical cases presented here had corneoscleral trephinations because time was lost while medical control was attempted. After the acute attack, Case 1 followed the course described by Posner and Schlossman,[10] establishing itself as a chronic, narrow-angle glaucoma. In view of the similarity of Case 2, it was again decided that surgery was best. The gradual lens changes which followed surgery in the first case were disappointing and may cause difficulties later.

In Case 3, the treatment followed classical lines. Neither the treatment nor the result was particularly unusual.

In order to prevent these attacks, Snydacker[14] has established five general rules which are extremely important to all those who use atropine or homatropine. Following these rules is time consuming, but, if these drugs are used, it is necessary to follow each rule in turn.

Summary

1. Three cases of homatropine-induced acute glaucoma have been presented.

2. The chamber angle is important in controlling the trigger mechanism present in the eye.

3. In the three cases presented, homatropine permanently altered the ability of the eye to withstand the glaucomatous condition.

4. Routine medical treatment was followed in all cases, with corneoscleral trephinations being necessary in two of the cases within six weeks.

5. Tension and fields have been stabilized in all three cases for over four months by the treatment described.

6. The use of homatropine in the usual concentrations entails a definite risk of causing acute glaucoma even in the most cautious of hands.

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CORRELATION OF THE ANATOMIC FACTORS CONCERNED IN THE OPHTHALMOSCOPIC APPEARANCE OF RETINAL HEMORRHAGES*

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The diverse ophthalmoscopic appearances of retinal hemorrhages have a multiphased pathogenic background. It is doubtful that all related factors in the production of such hemorrhages have as yet been hypothesized. The correlation and interpretation of the known pathogenetic factors does not give a conclusive picture of the problem.

This paper will be limited to a consideration of the significant anatomic features of the finer retinal vessels and the role they play in the ophthalmoscopic appearance of various retinal hemorrhages. The work in this field has evolved from the classical descriptions of His through the studies of Fortin, Damel, and others to the present-day, detailed descriptions of Michaelson and Campbell. These works have pointed out the significance of the location of the finer retinal vessels in the morphology of the hemorrhagic retinopathies.

We are all acquainted with the general vascularization plan of the retina, so, for the sake of brevity, we shall pass it by to consider the more detailed vascular structure of the retina. It has been recommended that all ophthalmoscopically visible arterial vessels of the retina be designated as arterioles.[1]

The branches of the larger arterioles and venules form an interdigitating pattern as they run toward each other (fig. 1). They remain in the nerve-fiber and ganglion-cell layers until the precapillary vessels are reached. These precapillaries, in turn, respectively feed and drain the capillary plexuses of the retina. The precapillaries branch, as is seen in the diagrammatic representation from Michaelson and Campbell[2] (fig. 2), and, basically, the branched precapillaries fall into two groups.

One, the superficial group, remaining in the nerve-fiber and ganglion-cell layers, gives rise to a superficial capillary plexus which lies in the same plane as its parent vessels. The other precapillaries run almost vertically into the retina to give rise to the deep capillary plexus whose meshwork is confined to the plane at the junction of the inner nuclear and the outer molecular layer. The latter capillary net is the more dense and complex of the two and the intricacy of each increases as the venous precapillary is approached.

There is some anastomotic capillary connection between the superficial and deep nets, but, for the most part, these plexuses are two dimensional in form. Of interest and importance is the schematic representation of the distance from the larger arterioles at which the arterial precapillaries branch as compared to the junction of the venous, precapillary branches being closer to the venule. This, plus the aforementioned fact of the increased density and complexity of the capillaries near the venous precapillaries, gives rise to the relative capillary-free zone which is present on the arteriolar side of the retinal circulation.

As Michaelson and Campbell have so well demonstrated, there are areas of less and more complicated modification of the basic two-layered capillary nets which have just been reviewed.

A third plexus is formed at the inner boundary of the inner nuclear layer. It arises from capillary loops of the superficial plexus which have lost their two dimensional character. In the most superficial portion of the nerve-fiber layer, a fourth capillary plexus is

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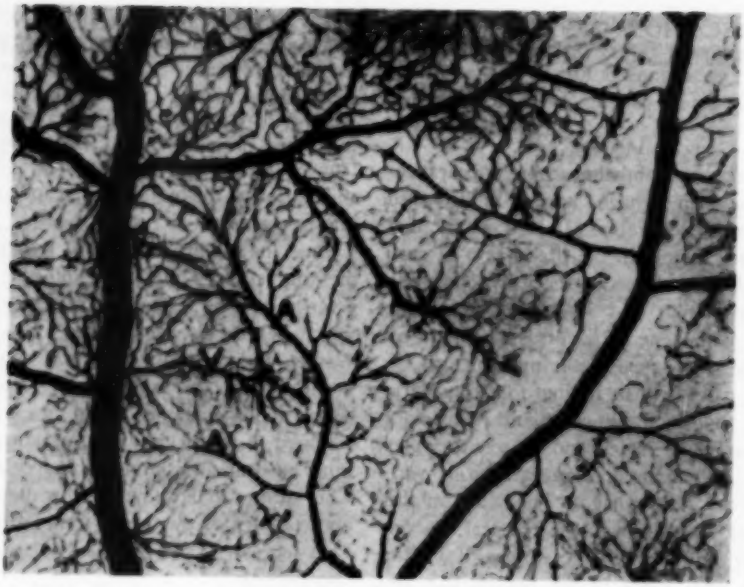

Fig. 1 (Smith). Field from equatorial zone of retina, showing a vein on the left and an artery on the right. Note the interdigitation of the venae efferentes (V) with the arteriae afferentes (A). Note also the capillary-free zone around the artery (×30). (Reprinted with permission from: Michaelson, I. C., and Campbell, A. C. P.: *Transactions of the Ophthalmological Society of the United Kingdom*, 1940.)

found. It arises from the precapillaries and capillaries of the basic superficial vascular layer. In the preëquatorial zone of the fundus, the plexuses are reduced to one, the superficial; and the peripheral one-mm. area is devoid of vessels. The distributions of these vascular patterns can best be represented by the schematic flat projection of the retina of the right eye (fig. 3) and consist of:[8]

1. The basic double capillary net, which occupies the retina of the posterior fundus to a point 12 to 14 mm. anterior from the optic disc.

2. The three-layer capillary zone of the perimacular area with its associated avascular foveal area.

3. The four-layer capillary meshwork of the peripapillary area, which extends four mm. nasally and seven mm. temporally from the optic disc. The temporal extent is indented in the horizontal meridian due to the presence of the macula.

4. The single-layer capillary (superficial) preëquatorial zone.

5. The avascular peripheral one mm. area.

The margins, as shown and enumerated above, are not hard and fast, but the various vascular structural relationships give way to each other gradually.

Pathologic considerations

The arrangement of the retinal vessels is an important factor in the pattern seen in the ophthalmoscopic appearance of retinal hemorrhages. The morphology of the hemorrhages is largely determined by their position in the retina, and this depends on the location of the vessels involved in the pathologic state. As was mentioned earlier, it does not clarify the whole of the problem, but it does help further the ophthalmoscopic differentiation of retinal hemorrhages in certain diseased conditions. Among the more common entities in which retinal hemorrhage are encountered are: hypertensive states, diabetes, papil-

ledema, central retinal or branch vein thrombosis, and blood dyscrasias.

HYPERTENSIVE GROUP

Retinal hemorrhages are frequently found in hypertensive states. They are primarily caused by the elevation of the blood pressure regardless of the initiating mechanism of the elevation.[4-6] Thus the hemorrhagic pattern is the same for all groups; that is, primary essential hypertension, both benign and malignant, arteriosclerosis, toxemia of pregnancy, adrenal gland tumor (pheochromocytoma), pituitary basophilic adenoma (Cushing syndrome), and the renal group of acute, subacute, or chronic glomerulonephritis, unilateral atrophic kidney, hydronephrosis, pyelonephritis, prostatic obstruction, and so forth.

The interpretation of the functional pathology of hypertension is without uniform opinion, but the essence of the condition, be it primary or secondary from an etiologic point of view, apparently lies in the spasm or increased tonicity of the arterioles.

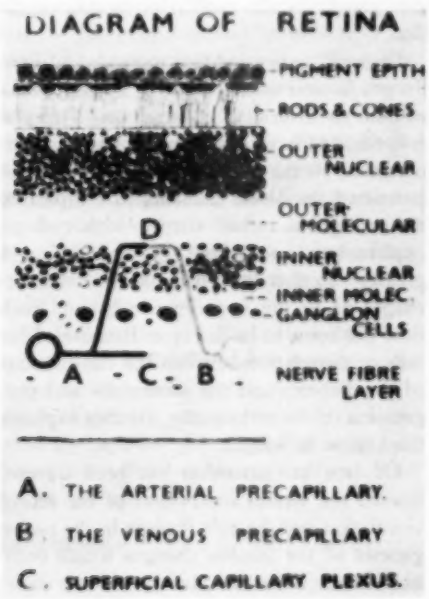

Fig. 2 (Smith). Diagrammatic representation of the situation of the superficial and deep capillary network. (D) in the figure represents the deep retinal capillary plexus. (Reprinted with permission from: Michaelson, I. C., and Campbell, A. C. P.: *Transactions of the Ophthalmological Society of the United Kingdom*, 1940.)

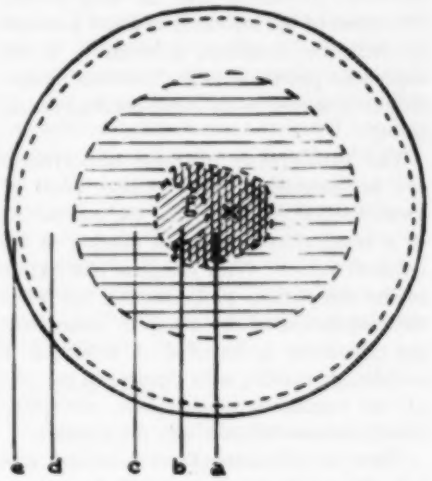

Fig. 3 (Smith). A flat projection of the right retina (×2). (x) Nervehead. (F) Fovea. (a) Extent of radial peripapillary capillary net. (b) Extent of triple capillary net. (c) Extent of double capillary net. (d) Extent of single capillary net. (e) Peripheral avascular zone. (Reprinted with permission from: Michaelson, I. C., and Campbell, A. C. P.: *Transactions of the Ophthalmological Society of the United Kingdom*, 1940.)

The retinal hemorrhages seen in this group are characteristically, but not exclusively, flame-shaped, due to their location in the linearly directed nerve-fiber layer. Due to the increased density of the nerve-fiber layer in the perimacular and peripapillary areas, the flame-shaped form of these hemorrhages is here more marked. In the equatorial zone of the retina, the relative looseness of the fibers permits the hemorrhages to assume a more irregular shape with the long axis lying in the direction of the nerve fibers.

An explanation for the apparently singular involvement of the superficial vessels in the production of the hemorrhages must be sought. Various hypotheses have been offered: (1) The constriction of the arterioles and capillaries leads to secondary changes in their walls permitting the escape of blood

elements to form hemorrhages; (2) the superficial plexus with its precapillaries is located "higher-up" in the vascular circuit and has a more direct relationship to the arteriolar circulation than the deep plexus. The effect of the increased vascular pressure is, therefore, manifest, principally, in the superficial plexus, with the resultant hemorrhages occurring in the corresponding retinal layer.[7]

The pathogenesis of these hemorrhages can be considered from another point of view. Ricker[8] observed that the contraction of a small artery results in dilation of the terminal vessels. With complete obstruction to the circulation, stasis results, but when the contraction of the artery is incomplete, the circulation is impeded. A reduction in metabolism results, with changes in the wall of the capillaries taking place, permitting blood elements to pass into the tissues.

Thus, the arteriolar spasm associated with hypertension may result in dilation of the retinal capillary plexuses with secondary changes taking place in their walls. Each capillary net would therefore be capable of losing blood cells into the tissues.

Perhaps the choriocapillaris blood supply to the outer retinal layers aids the deep plexus in its metabolism sufficiently to keep its capillary walls in a state healthier than the superficial plexus is able to achieve. This difference in the relative nutritional state of the capillary beds could account for the greater frequency of the flame-shaped hemorrhages of the nerve-fiber layer seen in the hypertensive group of patients.

Diabetes

As ophthalmologists, we recognize the typical ophthalmoscopic appearance of diabetic retinopathy; however, controversy exists as to whether or not this is a specific entity.[9-10] On the basis of recent work,[11-19] there seems to be little doubt that diabetic retinopathy is a condition distinct from hypertensive retinopathy. The fundi in the two conditions are distinguished by the difference in the mode of onset, location and type of lesions and hemorrhages, and in the development and termination of changes in the retinas.

The typical hemorrhages which occur in diabetes are round or dotlike, but occasionally flame-shaped hemorrhages are seen concurrently. Histologically, the round hemorrhages are located in the inner nuclear and outer molecular layers of the retina in the posterior fundus. They assume their round shape because of the looseness of the outer molecular layer into which the blood extravasates. Small microaneurysms may develop in the inner nuclear layer from the anastomotic capillaries and cannot be differentiated clinically from the hemorrhages.[20-21] They may be hemorrhages first, with endothelial cells coming to line them later.[22] Because of their location, the hemorrhages must arise from the deep capillary plexus. A uniformity of opinion exists as to the significance of the role played by the capillaries in this condition.

Duggan[23] suggested that increased adrenalin production secondary to a hypoglycemia caused an arteriolar constriction. This, he felt, resulted in capillary anoxia with changes occurring in the vessel walls; these changes permitted the blood elements to escape into the contiguous retinal tissue. With such an explanation, one would expect to find a greater number of flame-shaped hemorrhages as in the hypertensive group. Such does not seem to be the case. Because of the lack of correlation between the clinical state of the diabetes and the occurrence and progression of the retinopathy, further explanations must be sought.

Of late, our attention has been directed toward the venous component of the retinal circulation and the role it plays in the pathogenesis of the fundus changes which occur in diabetes. The accumulating evidence shows the vascular changes in the retinas of diabetic patients tending to affect the venous rather than the arterial side of the circulation.[24-26]

The fullness of the retinal veins in these fundi is recognized as one of the significant

findings.[27-29] It is interpreted as an early retinal change in diabetic patients.

Thus, the normally slower blood flow, in the more dense and relative circulatory-dependent deep capillary plexus, has the added congestion produced by the increased venous back-pressure as manifested by the dilated retinal veins. This results in a greater metabolic disturbance to the capillaries of the deep plexus than to the superficial plexus, and in part explains the pathogenesis of the diabetic hemorrhages.

Retinal vein thrombosis

In this state, the increased venous back-pressure is manifest throughout the retinal capillary system. The hemorrhagic retinopathy depends upon whether it is a central or a branch-vein block, and whether the obstruction is partial or complete. Depending upon the degree of obstruction, the pyramiding occurrence of these hemorrhages is: first, in the deep capillary plexus with the small round hemorrhages; next, in the superficial capillary plexus with the small flame-shaped hemorrhages; then, in the venous precapillary vessels with the larger flame-shaped hemorrhages; and, finally, in the extensive hemorrhages resulting from the rupture of a larger vessel. Commonly, the most superficial plexus of the peripapillary area gives rise to hemorrhages in association with the above.

As Ballantyne and Michaelson have described[30] the hemorrhages are usually closer to the venules than to the arterioles. This results from the periarteriolar area being relatively capillary free, and the density of the capillary plexuses being greater near the venous precapillary.

Papilledema

The occurrence of hemorrhages in this condition is not consistent. They may be among the first of the signs to appear, or may be absent when the swelling has reached a marked degree.[31] Usually, they are present, and are superficial, close to the optic disc, and radiate from it. They originate in the peripapillary plexus of the most superficial layer. The pathogenesis of these hemorrhages[32] is akin to the central retinal vein occlusion already mentioned but of a lesser degree. The increased venous back-pressure apparently results from the compression of the central vein in the intravaginal space of the optic nerve. However, in mild cases, the edematous process in the area could involve the most superficial plexus directly and give rise to the hemorrhages. At times, there are additional hemorrhages of the types associated with a marked increase in the venous back-pressure. It is of interest to note that, clinically, the superficial hemorrhages correspond to the flat retinal projection scheme of this capillary layer.

Blood dyscrasias

Patients with blood dyscrasias frequently show retinal hemorrhages. The dyscrasias which are of primary interest to the ophthalmologist include the main types, namely, anemias, leukemias, purpuras, and the polycythemias. The hemorrhagic extravasations are not sufficiently typical to permit an accurate and definite etiologic diagnosis with the ophthalmoscope. Although they may vary in form, their differences are a result of the mechanism of their production, rather than the particular disease entity with which they are associated.[33] The basic factors in the pathogenesis of these hemorrhages include the thrombocytopenia of the purpuras, the increased capillary permeability of toxic, anoxic, metabolic, or chemical origin of the anemias, and the venous stasis and thrombosis of the leukemias and polycythemias.

Thus, from the appearance of retinal hemorrhages alone, accurate differentiation cannot be made between the blood dyscrasias.

Summary

Fundus studies conclude a relationship between certain disease entities and their associated retinal hemorrhages. Analysis of these hemorrhages is facilitated by their

correlation with the anatomy of the finer retinal vessels.

Hypertension, diabetes, central retinal vein obstruction, and papilledema present basically characteristic hemorrhagic patterns. Other diseases, such as blood dyscrasias, trauma, and local retinal inflammatory states, produce hemorrhagic patterns which are not type specific.

The hypothesis is offered that the "double" vascular supply to the deep retinal capillary plexus area keeps these vessels in a state healthy enough to prevent local hemorrhages in the hypertensive patients. Thus, the singular nutritional supply to the superficial vascular plexus permits hemorrhages to occur more readily in patients of this group.

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NOTES, CASES, INSTRUMENTS

A CASE OF RECURRENT IRITIS AND EPISCLERITIS ON A RHEUMATIC BASIS TREATED WITH ACTH*

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The recent use of adrenocorticotropic hormone (ACTH)† experimentally in the treatment of rheumatic fever, rheumatoid arthritis,[1, 2] and other collagen diseases has attracted widespread interest in the scientific and lay press. The frequency with which recurrent iritis is associated with these conditions, especially with rheumatoid arthritis, points to an intimate relationship, the mechanism of which has been at best imperfectly understood.

We report herewith a case of recurrent iritis and episcleritis on a rheumatic basis with prompt improvement of symptoms following treatment with ACTH. What the subsequent course will be now that the therapy has been discontinued remains to be seen. Three weeks after treatment has been stopped the condition is excellent but it is not unlikely that a further recurrence may be expected at a later date.

CASE REPORT

History. Mrs. O. H. B., aged 34 years, was first seen at the office on September 29, 1949, with a history of pain, redness, and photophobia in the left eye of 10 days' duration. There was a history of two previous attacks of iritis in the left eye, four and two years ago. Health has been satisfactory except for a history of rheumatic fever in childhood, with an acute exacerbation five years ago and fleeting pain and swelling in various joints periodically since. During the previous attacks of iritis, general examination had revealed no other etiologic factor.

Eye examination. Visual acuity was 20/12 in the right eye and 20/25 − 3 in the left. The right eye was normal grossly and with the slitlamp. The left eye showed a moderate ciliary injection and was moderately tender. The pupil was somewhat irregular, constricted, and the iris darker than the fellow. Examination by biomicroscopy revealed an aqueous flare and numerous fine keratic precipitates. A diagnosis of recurrent iritis, left eye, was made.

Atropine and neosynephrin (10 percent) were instilled. The pupil dilated well except from the 4- to 7-o'clock positions where the pupillary margin of the iris was adherent to the lens capsule. Atropine and heat were ordered locally, sodium salicylate was prescribed internally, and a complete general check-up advised. Physical examination at that time did not reveal any positive findings except for changes in various joints, classified as arthritic.

Under local treatment the iritis continued to improve so that in one month the eye appeared quiet and only a few old precipitates were seen on the corneal endothelium. On October 29th, because of a story of occasional discomfort in the left eye, all treatment was discontinued except for atropine once a day in the left eye. The tension was at all times normal.

Two days later, on October 31st, the patient returned with a complaint of redness and pain in the right eye. There was a slight suggestion of ciliary injection but no definite cells or other evidences of iritis were seen. Homatropine was instilled and the patient kept under careful observation. By November 7th, there was a marked ciliary injection,

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† We are indebted to the Armour Laboratories who through Dr. John Mote so kindly furnished the pituitary adrenocorticotropic hormone (ACTH) used in this study.

aqueous flare, cells in the aqueous, and a few small diffuse keratic precipitates. Atropine, heat, and salicylates were prescribed.

The course of the iritis was slow but progressive in the right eye, but the left eye remained inactive and atropine was discontinued in the left eye on November 14th. The right pupil dilated well under atropine. By November 21st the iritis in the right eye had continued to increase and hospitalization was advised in order to carry out a more thorough investigation and possibly resort to foreign-protein therapy.

Hospital course. Mrs. O. H. B. was admitted to Wesley Memorial Hospital on November 23rd. Her chief complains on admission were pain and redness of the right eye; tenderness, pain, and limitation of motion of the left shoulder; swelling and pain in both knees with fluid in the left prepatellar bursa; tenderness and swelling of the right great toe.

Her temperature on admission was 99.6° F., pulse 90, respirations 20, blood pressure 130/90 mm. Hg. The only significant finding outside of her arthritis from a medical point was a soft apical systolic murmur which was also heard over the aortic area. The tentative diagnosis on admission was an old rheumatic endocarditis and an early acute rheumatoid arthritis.

During the first few days in the hospital while the patient was undergoing the general examination and observation, and receiving only atropine and heat to the right eye and sodium salicylate internally, there developed a severe episcleritis to the temporal side of the left eye, without any evidence of a recurrence of the iritis in that eye, but the iritis in the right eye continued to be severe but without any hypopyon or synechias developing.

The laboratory findings at this time were as follows: R.B.C., 5,070,000; Hemoglobin, 97 percent; hematrocrit, 39.4; W.B.C., 21,000; differential N., 75; neutrophil unseg., 5; lymphocytes, 17; monocytes, 2; erythrocytes, 1; uric acid, 3.84; N.P.N., 26; total proteins, 7.18; albumin, 3.62; globulin, 3.45; urine: sp. gravity, 1.030; acid, albumin, 20 mg., sugar negative; R.B.C., 5-6, W.B.C. 8-10; E.K.G.: Frequent premature systoles of nodal origin. X-ray studies of the chest showed the cardiac silhouette to be normal, the lung fields clear. X-ray films of the hands showed changes compatible with an early rheumatoid arthritis.

ACTH therapy. At this stage it was decided to administer pituitary adrenocorticotropic hormone (ACTH). This was started on December 12, 1949. Ten mg. were given intramuscularly every eight hours, at 8 a.m., 4 p.m., and 12 p.m. The dosage was then decreased to 20 mg. daily in three divided doses at the same intervals, and was continued through December 23, 1949. Again the dosage was decreased to 10 mg. daily at 12-hour intervals, at 8 a.m. and 8 p.m. This procedure was continued through December 31, 1949, at which time the hormone was discontinued.

The patient remained in good electrolyte balance during the entire course of her treatment. The swelling and pain in both knees disappeared. Pain and tenderness in the left shoulder were relieved in approximately 72 hours. However, she continued to complain of pain in the right great toe. The temperature returned to normal in 12 hours after ACTH and remained so until her discharge from the hospital. The sedimentation rate (47, on admission) had returned to 21.

Almost immediately (within 36 hours) the episcleritis had practically disappeared and the iritis showed marked improvement so that within one week there remained no active iritis. The treatment was continued for 29 days without any return of the episcleritis or iritis.

Examination of the eyes three weeks after the therapy had been discontinued showed no injection in either eye. Biomicroscopy showed a few fine scattered deposits remaining on the corneal endothelium of the right eye, practically none in the left, and no evidence of any active pathologic process in

either eye. The right pupil was of normal size and reacted readily, the left showed only the adhesions between the iris and lens capsule seen on the first examination. There was marked improvement in the patient's general condition with joint symptoms reduced to a minimum.

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PROJECTION TACHYSTOSCOPE FOR ORTHOPTIC TREATMENTS*

A PRELIMINARY REPORT

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Recently Burian[1] reported on the use of projection in orthoptic treatment. As a result of interest in this same idea, I have developed a projection tachystoscope for orthoptic treatment. This instrument consists of:

a. A Leitz "Kleinbild" projector (VIIIs).

b. Slides resembling the ordinary object slides used with the major amblyoscope of Hamblin. Instead of colored pictures, however, drawings are made with black ink on white paper. These drawings are photographed, and the negative, showing white-lined pictures on a black background, is mounted on a lantern slide. The pictures for the right and left eyes are mounted side by side (fig. 1).

c. At a distance of approximately 20 cm. in front of the objective of the Leitz projector, there is a screen (fig. 2), 19 by 15 cm., with two holes 3.5 cm. in diameter. The distance between the middle points of these holes is 5 cm. A rotating double prism of Risley is placed anteriorly to each hole, and a polaroid disc is mounted posteriorly. The polaroid discs may be rotated so as to adjust the direction of the polarized light.

d. Between the objective of the projector and the screen, there is a large disc, 22 cm. in diameter, with two semicircular slits (fig. 3). This disc is rotated by a motor with a variable speed that is measured by a revolution counter. The disc acts as a tachystoscope. The light from each of the separate pictures on the slide is interrupted alternately.

Fig. 1 (Winkelman). Object slides.

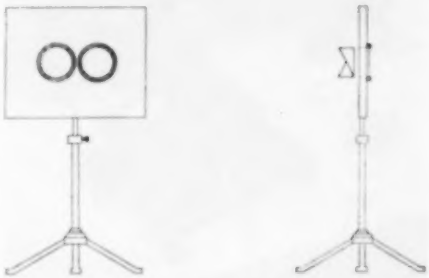

Fig. 2 (Winkelman). Screen with rotating double prisms and polaroid discs.

e. The pictures are projected onto an aluminized screen and the patient observes them through polaroid spectacles. A com-

* From the Eye Clinic of the University of Amsterdam, Dr. A. Hagedoorn, director.

plete arrangement of the apparatus may be seen in Figure 4.

Method of treatment

This apparatus has been installed in a special room which can be completely darkened and which can be divided by a drop curtain into two separate parts.

Fig. 3 (Winkelman). Tachystoscope discs with semicircular slits.

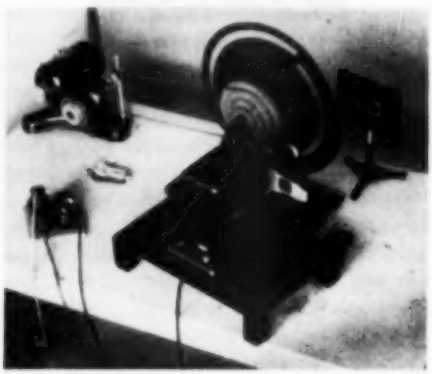

Fig. 4 (Winkelman). Photograph showing the different parts of the apparatus.

One of these parts is of small dimensions and contains the apparatus. No light can filter from this cubicle except through an opening in the curtain which permits the light from the projector to fall on the aluminized screen (fig. 5). This cubicle may be illuminated at convenience.

The patient sits in the other part of the room, which is completely darkened. Complete darkness must be particularly stressed, for it is essential that no stimuli, other than those intended for the stimulation of both maculas, fall on the patient's retinas.

The polaroid spectacles with which the patient is provided are so adjusted that only the eye intended will be stimulated by the picture projected for this eye.

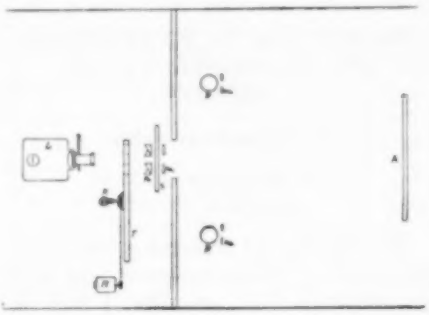

Fig. 5 (Winkelman). Diagram of test arrangement and dark room. (A) aluminized screen; (L) Leitz projector; (M) motor; (P) patients; (Po) polaroid; (Pr) prisms; (R) revolution counter; (S) screen; (T) tachystoscope disc.

The rotating double prisms are adjusted so that the projections on the aluminized screen are at a distance from each other corresponding to the angle of squint. Since this arrangement is not suitable for very large angles, it is necessary, in such an event, to reduce the angle by inserting prisms before the patient's eyes.

With this apparatus, it is possible to stimulate haploscopically the maculas, and nothing but the maculas, and to carry out the ordinary exercises for orthoptic training.

We can establish Grade-I fusion or simultaneous perception by using Grade-I slides. We can exercise fusional amplitudes by rotation of the Risley double prisms. For these exercises, the tachystoscope disc is removed.

When we wish to overcome abnormal retinal correspondence, we can stimulate the macula of each eye alternately by interposition of the tachystoscope disc. The light rays from one of the pictures pass through the semicircular slit, while those from the other are temporarily interrupted. In this manner, the pictures for the left eye and for the right eye are exposed alternately.

By lowering or raising the speed of the motor, the speed of the alternating stimulation can also be varied. The instrument can be further improved by connecting a second motor to one of the rotating double prisms. One of the pictures can then be moved mechanically across the macular field of one eye. This is beneficial in treating abnormal retinal correspondence.

Suppression may be easily overcome by the use of this apparatus. I have examined several patients who were unable to obtain Grade-I fusion (simultaneous perception) with the major amblyoscope but who obtained simultaneous macular perception at once with this arrangement. It is ideal for examination of patients with more or less pronounced amblyopia of one eye.

It is interesting to notice that the fusional amplitude in normal persons appeared smaller with this apparatus than in the major amblyoscope. Perhaps it is the total absence of peripheral stimuli (the rôle of which was first stressed by Dr. Burian in his ingenious experiments[2]) that causes the decrease of fusional amplitude.

Our instrument may be more helpful in overcoming abnormal retinal correspondence than the ordinary devices. I have tried the apparatus in children after operation. In several instances where the orthoptoscope of Hamblin had failed to demonstrate Grade-I fusion, simultaneous macular perception with normal correspondence could be established in one session.

When the eyes are straightened by operation, it is possible to train more patients simultaneously; when the angle of squint is corrected by prisms, it is also possible to exercise several patients at a time before operation.

I have not yet obtained sufficient data to demonstrate clearly the advantage of this arrangement over the ordinary methods of orthoptic treatment, but the cases I have examined have already convinced me that this method will throw a new light on several problems connected with squint and that it is a most valuable aid in the examination and treatment of strabismus patients with suppression.

Wilhelmina-Gasthuis.

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GLIOMA OF OPTIC NERVE

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According to reports reviewed, glioma is the most common tumor of the optic nerve; however, it is still rare as evidenced by a review of 669,857 patients at the Massachusetts Eye and Ear Hospital,[1] in which four such tumors were removed during a 36-year period. DeLong,[2] at Wills Hospital, Philadelphia, reported only one such tumor in 230,742 patients, over a 12-year period.

This case is presented with reference to the operative approach and pathologic classification. Review of the literature by Hudson,[3] in 1912, reveals 182 cases; Mannheimer[4] reported one case in 1940; Katzin,[5]

one case in 1945; Wilson and Farmer[6] reported two cases in 1940; Rueling[7] reported one case in 1943.

As pointed out by Wilson and Farmer, these tumors are divided into two large groups: (1) The dural endotheliomas or meningiomas which arise from the fibrous sheath of the nerve, and (2) the gliomas which arise from the neuroglial elements within the nerve itself. This case falls into the latter group.

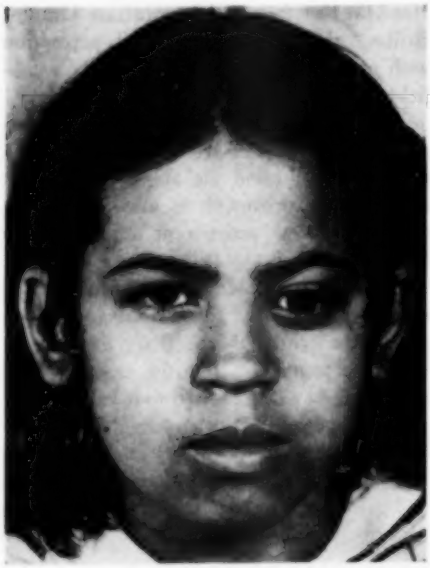

Fig. 1 (McFarland). Appearance of patient at time of first examination.

Report of case

History. E. V., nine-year-old Mexican girl, was first seen February 2, 1948, with the complaint of a protruding left eye of three years' duration. The left eye was also turning outward (fig. 1). The girl complained of poor vision in the left eye and occasional headaches. There was no ocular pain at any time, no history of injury or of disease.

Eye examination. The right eye was normal. The left eye revealed a marked proptosis, and pointed down and slightly outward. There was inability to move the left eye superiorly. There was no pulsation or tenderness.

Exophthalmometer readings: O.D., 14 mm.; O.S., 17 mm. Vision: O.D., 20/20; O.S., no light perception. Cornea: O.D., normal; O.S., suggestive corneal hypesthesia. Pupils: O.D., round, reacted to light, fundus normal; O.S., round, slightly larger than left; no reaction to light; consensual reflex present. Serology: negative.

Ophthalmoscopy: O.D., normal; O.S., lens and media clear; disc—white with lamina cribrosa visible; blood vessels were smaller than normal; no retinal lesions visible.

Fields: O.D., normal, peripheral and central, with 3/300 white test object and 1/1,000 white test object; O.S. No light perception.

Roentgenograms revealed the left foramen to measure nine mm. in greatest diameter, the right foramen, four mm. No pathologic condition of the bone in the orbits was evident. Neurologic examination, negative.

Diagnosis. Primary optic atrophy, left eye. Probable optic-nerve tumor.

Since the X-ray findings seemed to indicate that the intracranial part of the optic nerve was involved, it was decided to make an intracranial section of the nerve prior to enucleation. The preoperative diagnosis was glioma, optic nerve, left eye.

Operation. On March 2, 1948, under endotracheal anesthesia, a concealed horseshoe-shaped incision was made in the left frontotemporal region of the scalp. The bone flap elevated with no technical difficulty. The dura was separated from the roof of the orbit to the sphenoid ridge and incised. The left optic nerve was identified. It was found to be larger than the right, which was also examined, and gray-red in color.

The roof of the orbit was removed medially to the ethmoid sinus and laterally to its lateral wall. The bone was removed to and including the roof of the optic foramen.

Part of the left optic nerve was incised. The neoplastic involvement of this structure extended intraorbitally. After the orbital contents were incised, the optic nerve was traced to the globe and a section was taken for microscopic study. The wound was closed in layers, and the scalp was sutured with interrupted silk sutures. An alcohol dressing was applied and a drain placed in the inferior angle of the wound.

After a microscopic diagnosis had been obtained and the prognosis of the child's condition discussed with her parents, additional surgery was done.

On March 25, 1948, the wound was reopened. Through the same exposure, the left optic nerve was identified, resected one-eighth inch anterior to the chiasm, and then dissected forward. Approximately one-fourth to one-half inch of the nerve was removed and the nerve was freed at its attachment to the optic foramen so that enucleation and removal of the tumor, which extended into the orbital portion of the optic nerve, would be possible.

On April 6, 1948, under ether anesthesia, enucleation of the left eye was performed. The optic nerve was found to be very large in size and had a grayish, spindle-shaped appearance. Considerable difficulty was encountered in removing the nerve and globe. Tumor changes were present at the cut end of the nerve.

Pathologic report. Several sections show a uniform picture of what appears to be glial tissue with considerable fibroglia present. The tissue is unusually cellular. The nuclei are uniform in size and shape and have a sparse chromatin material which is coarsely divided and diffusely scattered through the nuclei. There is no tendency to palisading or actual whorl formation, and no evidence of a neurofibromatous type of growth.

There are numerous blood vessels which, apparently, have no tendency to endothelial proliferation. In some areas, the glial cells radiate toward the blood vessels, and fibrils are found extending to the inner surface. The gliomatous growth extends to the opening of the optic nerve in the sclera, but the nervehead itself is not obtained on the section. There is considerable old granulation tissue in this area which is not neoplastic. Diagnosis: Glioma of the optic nerve.

Fig. 2 (McFarland). Enucleated eye with resected optic nerve.

Comment

The history in this case is characteristic—gradual loss of vision, slow development of exophthalmos, and no ocular pain. In this case, there was optic atrophy and complete loss of vision by the time surgery was performed.

Verhoeff pointed out that gliomas were an overgrowth of glial tissue and were the only primary intraneural tumors of the optic nerve. They have no relation to the common malignant tumor of the retina called "Glioma." Verhoeff[8] also reported on the histologic examination of these tumors. He states that gliomas do not increase in size by invading or destroying the original nerve structure, but enlarge by proliferation of the neuroglia in the vicinity of the growth. Gliomas of the optic nerve have no tendency to return even after incomplete removal.

Fields in the right eye of this patient, taken at regular intervals since the operation, have remained normal. Cranial nerves, with the exception of the second, have functioned adequately. Cerebral and cerebellar function has remained intact. Motor and sensory systems have revealed no abnormalities.

509 West McDowell Road.

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HIGH HYPERMETROPIA

Report of two cases

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In reviewing the literature, I found only one reported case of hypermetropia that was as high as two cases which have come to my attention. Tirelle,[1] in 1947, reported the case of a six-year-old boy who wore a +16.0D. lens, R.E.; and a +17.0D. lens, L.E.; visual acuity with correction was: R.E., 2/10; L.E., 1/10.

Lambert and McDannald,[2] in 1931, reported five cases, a mother and four children, with hypermetropia ranging from +6.50D. to +10.0D. Convergent squint was present in some of their cases.

Case reports

I wish to report two cases of high hypermetropia in sisters who, otherwise, are perfectly normal, attractive little girls.

Case 1

History. G. G., aged six years, was referred on November 12, 1948, by the school nurse who discovered her condition in a routine check of school children. The child always held her reading material close to her face and sat in the front row in school. Her school work, however, was apparently satisfactory.

Physical findings. The patient was a normal child in every respect except for her eyes.

Eye examination. Without correction, vision was: R.E., 20/200; L.E., 10/200. Externally normal. No muscle imbalance. No microphthalmia. Under atropine sulfate cycloplegia, the fundi appeared to be normal; the lenses were proved to be present by the Purkinje images and slitlamp examinations.

Retinoscopic examination showed: R.E., +15.0D. sph., L.E., +15.0D. sph. Subjective refraction: R.E., +15.0D. sph. ⌒ +0.5D. cyl. ax. 90° = 20/70; L.E., +15.0D. sph. ⌒ +1.0D. cyl. ax. 90° = 20/200. Prescription: R.E., +13.0D. sph. ⌒ +0.5D. cyl. ax. 90° = 20/70; L.E., +13.0D. sph. ⌒ +1.0D. cyl. ax. 90° = 20/200.

Case 2

History. M. G., aged 12, years, was first seen on December 11, 1948. In 1947, she had been seen by Dr. Thurber Le Win, Buffalo, New York, who had prescribed the glasses she was wearing.

Physical findings. Except for her eyes the girl was normal in every respect.

Eye examination. Without correction, vision was: R.E., 7/200; L.E., 7/200. Externally normal. No muscle imbalance. No microphthalmia.

Under homatropine cycloplegia the fundi appeared to be normal; lenses were proved to be present by the Purkinje images and slitlamp examinations.

Retinoscopic examination showed: R.E., +16.0D. sph. ⊂ +2.0D. cyl. ax. 75°; L.E., +16.5D. sph. ⊂ +2.0D. cyl. ax. 105°. Subjective refraction: R.E., +16.0D. sph. ⊂ +2.0D. cyl. ax. 75° = 20/200. L.E., +16.5D. sph. ⊂ +2.0D. cyl. ax. 105° = 20/200. Prescription: R.E., +16.0D. sph. ⊂ +2.0D. cyl. ax. 75° = 20/200; L.E., +16.5D. sph. ⊂ +2.0D. cyl. ax. 105° = 20/200.

This child is wearing the full homatropine findings.

A third sister wears glasses but is only moderately hypermetropic, and the parents' eyes are not remarkable.

302 Professional Building (13).

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FURTHER STUDIES OF STEVENS-JOHNSON'S DISEASE*

Report of two cases with purulent conjunctivitis, stomatitis, and cutaneous eruption

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Buffalo, New York

In 1946, in presenting a case of Stevens-Johnson's disease, we reported some etiologic studies of the disease. We now wish to report two additional cases in which the studies were continued, with special attention being paid to signs, symptoms, and laboratory work.

The signs and symptoms of Stevens-Johnson's disease are acute onset, with headache, anorexia, chilly sensations, fever, joint aches, coryza, bronchitis or bronchopneumonia, mental confusion, and moderate to severe deafness.

The skin generally exhibits macules, papules, and vesicles which may also be found on the buccal surfaces, palate, vaginal mucosa, and glans penis. There is a severe purulent conjunctivitis and stomatitis.

The marked constitutional symptoms serve to distinguish this disease from the erythema multiforme which von Hebra first described in 1886.[1] Patients with Stevens-Johnson's disease are acutely ill and once the disease is seen, recognition is not difficult. The etiology is unknown.

* From the Department of Ophthalmology, University of Buffalo Medical School, and the Edward J. Meyer Memorial Hospital.

Case reports

Case 1

History. C. W., a housewife, age 37 years, born of Polish parents, was admitted to the hospital acutely ill on November 19, 1947.

She was married and had two children. Her personal and past histories are not relevant to the present illness.

The onset of the disease was about five days before admission. She noticed that she got chilly following a hot bath. That night her eyes felt sore and became red. The next day her mouth was sore and blisters appeared on the inner cheeks and roof of the mouth. A productive cough developed, with difficult breathing, malaise, weakness, burning on urination, and vaginal discharge. Red spots developed upon the skin. Her physician prescribed penicillin for two days without relief. She then came to the hospital.

Physical examination. At admission she presented a diffuse bilateral conjunctival injection with some purluent discharge. There were ulcerated areas of the mucosa of the mouth, pharynx, and fauces.

The nares were reddened with hemorrhagic areas on the septum. There were scattered ulcerated areas of the mucous membrane of the tongue and cheeks. No adenopathy in the neck was found. There was a

profuse vaginal discharge with tenderness, making vaginal examination difficult. The skin showed a bilateral papular eruption generalized over the entire body.

Summary of laboratory work. Urine: one-plus albumen; many epithelial cells. Blood: Leukopenia; Wassermann—negative. Feces: Occult blood, one plus. Sputum: Negative. Blood cultures: No growth. Sedimentation rate: 42 to 50—one hour (increased). Spinal fluid: Chlorides, 640 mg./100 cc.; sugar, 55 mg./100 cc. X ray: Increased markings in both bases.

Eye examination. The eyelids were markedly edematous, almost closing the palpebral aperture. There was a moderate amount of purluent exudate in the conjunctival sac flowing out on to the face and matting the cilia. The bulbar conjunctiva was injected, edematous, and chemotic. Both corneas were clear. The pupils reacted normally. The iris appeared to be normal, as did the anterior chamber. Fundus examination was impossible because of edema and excoriation of the lids. Vision was markedly reduced in each eye.

Treatment—The patient was treated symptomatically and, after about 11 days, temperature dropped and she began to improve. Sulfathiazole (5 percent) ophthalmic ointment was used in each eye. She was discharged at the end of six weeks to return to the out-patient department.

During this time the right cornea developed an opacity at the limbal area at about the 5-o'clock position. The left eye was clear. The conjunctiva remained beefy red with a slight amount of discharge for several weeks and, at the end of four months, still showed some injection and discharge. At the end of three months the corneal infiltrates in the right eye had increased and vision was reduced to counting fingers at two feet. Vision in the left eye was 20/50 uncorrected.

At this time the eyes are quiet and clear except for residual scars in the right cornea. Vision is still reduced in the right eye. The skin and mucous membranes show slight pigmentary changes.

CASE 2

History. R. B., a 47-year-old white woman, was admitted to the hospital June 29, 1948. She was comatose and the following history was obtained from her husband:

She had been quite well and had no recent medication except for some treatment for obesity. Four days before admission she had had fever and chills, nausea and emesis, and a generalized rash and drowsiness. Her physician had then given her penicillin. She grew worse and was brought to the hospital.

Physical examination. At admission she was semiconscious, breathing deeply and regularly. Her skin presented a generalized maculopapular eruption on the face, arms, legs, shoulders, and back. The mucous membranes of the mouth were ulcerated. There was a purulent conjunctivitis. One or two nodes were palpable in the neck. No other adenopathy was found.

The chest showed some dullness on the right side with a few moist rales. The heart was regular. No other physical findings were relevant.

Summary of laboratory work. Urine: one-plus to negative albumen; negative to trace of glucose; rare pus cell. Blood: Urea 90, 78, 81, 34, 17; CO_2, 40 to 56; sugar, 104; hemoglobin, 13 gm.; white blood count, 26,700, 91 percent of polymorphomuclears; bleeding time, 2½ minutes; clotting time, 1½ minutes; prothrombin, 20; control, 17; Wassermann—negative; blood cultures showed Staphylococcus albus anhemolyticus. Cultures: Nose and throat, negative for diphtheria; conjunctiva, a negative coagulose-type Staphylococcus.

On the second day of her hospital stay, the patient was quite clear mentally and responded promptly.

Eye examination. The eyes showed moderate beefy red injection and chemosis of the conjunctiva, especially the bulbar portion. There was a moderate amount of purulent

discharge in the conjunctival sac with matting of the lashes. The skin of the lids showed maculopapular lesions which later become scaly and pigmented. The pathologic process in the right eye showed a grayish haze which was densest at the lower nasal quadrant and involved the pupillary area. The patient gave a history of a keratitis in childhood which left her with scars and reduced vision.

The left cornea remained clear throughout this illness. Vision was 20/200 in the right eye; 20/20 in the left eye.

On the 11th day, the temperature dropped sharply; improvement was rapid, and the patient was discharged from the hospital on January 20, 1948. She returned to her home which was in another city and further study was not possible.

Investigations*

We did two types of investigation:

Type 1

We examined epithelial scrapings for inclusion bodies, daily.

Examination of epithelial scrapings from the conjunctivas and from the vagina when stained with Wright's or Giemsa stain failed to show the presence of inclusion bodies in either Case 1 or Case 2.

Type 2

The serum was examined in the manner previously described[2] for the presence of psittacosis antigen in the 2nd, 5th, and 10th week of the disease.

The examination in Case 1 showed no complement fixation of the patient's sera in the presence of psittacosis antigen in any dilution. Examination in Case 2 showed complement fixation of the patient's sera in the presence of psittacosis antigen in serum dilution 1:2 (4 plus) and 1:4 (1 plus) in the second week of the disease.

*I wish to thank Dr. Karl F. Meyer of the Hooper Foundation, University of California, for examining the sera.

Discussion

The name Stevens-Johnson's disease should be restricted to cases which present purulent conjunctivitis without membrane formation, stomatitis, and cutaneous eruptions. There should be marked constitutional symptoms, anorexia, fever, malaise, sometimes deafness, and mental confusion. All other cases should be excluded from this classification.

We believe that this disease is caused by a virus of the psittacosis group, and report our findings in three cases with the hope that this investigation will be repeated by others.

Widerman[3] reported two cases. He believed that Stevens-Johnson's disease is a variant of erythema exudativum multiforme, but suggested the retention of the term Stevens-Johnson. Also he thought perhaps no single factor was responsible for the disease.

Wentz and Seiple[4] suggest that Stevens-Johnson's disease is not an entity but a variation of erythema multiforme exudativum.

Weisberg and Rosen[5] state that erythema exudativum multiforme is a single entity and should not be separated into symptom complexes. They feel that the disease is an avitaminosis.

Eger[6] reports one case and emphasizes the importance of recognizing the disease and its possible eye involvement. He attempts to clarify the terminology used to describe the disease.

Soll[7] reported 20 cases of eruptive fever. This is an excellent article but the cases are not typical Stevens-Johnson's disease. Kove[8] saw two cases and suggested a possible relationship of the disease to mumps.

It is seen that there is much confusion among observers as to the terminology of this disease. It seems to us that a simple classification of the types of erythema multiforme is desirable. To restrict the term Stevens-Johnson's syndrome would seem a good start.

There is considerable speculation as to the etiology of this disease, and more laboratory investigations are desired. This may be less difficult in the future, as it would appear that the disease is occurring more frequently.

SUMMARY

Stevens-Johnson's disease is rare. The etiology is unkown. We have presented a total of three cases. Two of these cases showed the presence of antibodies of the psittacosis group of viruses.

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ACUTE PORPHYRIA

ASSOCIATED WITH RETINAL HEMORRHAGES AND BILATERAL OCULOMOTOR NERVE PALSY

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Acute porphyria is a rare condition due to an error of metabolism. No more than 100 cases have been reported. Porphyrins are colored compounds which have a widespread natural occurrence. They are found in hemoglobin, chlorophyl, and most plants. When porphyrins are found in abnormal amounts in the tissues, urine, and blood, the condition is known as porphyria.

The porphyrias are divided into three groups: (1) Congenital, (2) toxic, (3) acquired idiopathic.

ACUTE TOXIC AND ACQUIRED IDIOPATHIC PORPHYRIA

These conditions appear to be the same except that the acute toxic form arises as a result of chronic poisoning. Most cases are due to sulfonal toxicity.[1] Cases have also been reported following lead, pyramidon, acetanalid, sulfonamide, glycerine, veronal, and trional administrations.[2] The idiopathic cases have been attributed to some congenital metabolic disturbance, but it is likely that toxic porphyria occurs in patients with this latent error of metabolism. Cases have been reported subsequent to infections and pregnancy. The cause in the case to be reported is probably no different.

Most cases have been observed in women between the third and fifth decades. However, it is not infrequent in men and children of both sexes. The prognosis is very poor, as many as 75 percent of the patients die during an acute attack. Most of the remainder succumb during subsequent attacks. Death has been attributed to bulbar involvement.[3]

The signs and symptoms of an acute attack are varied and involve numerous systems of the body. In a characteristic sequence, the patient first complains of severe abdominal pain associated with constipation. Mental changes are commonly found. These

consist of extreme restlessness and irritability. Convulsions are common. Total disorientation and coma are occasionally met with. Pigmentation of the skin is a frequent accompaniment.[4] The skin becomes yellow-brown or else yellow-brown spots appear on the neck and face. A characteristic skin lesion, hydroa vacciniforme, consists of vesicles or bullae and appears on the exposed surfaces of the body. There is marked weakness of the upper and lower extremities. Deep tendon jerks are diminished or absent. The abdominal reflex is occasionally absent. The patient may complain of pain in the extremities during the acute stage. According to Ford,[3] these patients do not show retrobulbar neuritis or oculomotor palsies. However, Harris[2] reported the occurrence of optic neuritis.

Upon standing, the urine becomes red or brown. Spectroscopic examinations for porphyrins are positive. Spinal-fluid examination is often normal but there may be increased amounts of globulin. Secondary anemia is common.

The duration of an acute attack is variable. It usually lasts 4 to 6 weeks but may last for several months. Recurrences are the rule.

The diagnosis is not a simple one if the urinary porphyrins are not observed. The acute abdominal pain in association with secondary anemia frequently leads one to suspect intra-abdominal bleeding.

Congenital porphyria is rare and makes its appearance early in life. It is similar to the type already discussed except that there is pronounced sensitivity to light (skin lesions) and splenohepatomegaly.

Case report

History. M. P., a 22-year-old white, married woman, was first admitted to the City Hospital with the major complaints of right lower quadrant pain, vomiting, and headache of one month's duration. For the past week she had had intense constipation unrelieved by milk of magnesia and cascara.

Her menses were regular. There was no weight loss. The patient was never pregnant. There was no antecedent infection. The remainder of the past history was noncontributory.

On admission the patient was pale, somnolent, and disoriented. Blood pressure was 100/60 mm. Hg. Pulse was 90. Temperature was 100.1°F. There were four small petechias on her abdomen. All deep tendon reflexes were absent. The abdominal reflex was also absent. Blood serology was negative. Blood count and prothrombin time were normal.

Ophthalmic examination revealed bilateral ptosis of the eyelids. Levator action was negligible on both sides. There was bilateral, incomplete oculomotor nerve palsy. The pupils were dilated and immobile to light or near stimuli. Both eyes could be abducted well. On attempted downward gaze, the eyes intorted, indicating good function of the superior oblique muscles. Convergence was impossible. Examination of the optic fundi revealed bilateral blurred discs and numerous hemorrhages which were nerve fiber, preretinal, and choroidal in distribution. Most of the hemorrhages were in the vicinity of the optic discs, the maculas, however, being spared. There was no retinal pallor or edema. The vessels were of normal caliber. There were no evidences of hypertensive retinopathy.

A specimen of urine accidentally found two days after collection was red-brown in color. A fresh specimen was examined four days after admission. An ether extraction was performed and studied under a Wood lamp. A characteristic red glow was observed. Spectroscopic examination was positive for porphyrins. This was subsequently confirmed several times. Blood examination was negative for porphyrins.

On the sixth hospital day the patient went into coma. On the eighth day she began to recover. The oculomotor palsies were clearing. On the 10th hospital day the patient was mentally clear. The oculomotor paralyses

were almost completely gone. Extraocular movements were normal in all directions of gaze. The patient exhibited an end-position nystagmus in the fields of action of those muscles supplied by the third cranial nerve. Most of the flame-shaped hemorrhages were gone and the others were absorbing readily. The pupils remained unresponsive. Several large bullae developed over the dorsum of both feet. Spectroscopic examination of the fluid from one of the bullae was negative for porphyrins. Three weeks after admission the patient was entirely clear mentally.

Comment

The signs and symptoms exhibited by this patient are consistent in most respects with a diagnosis of acute porphyria. There are, however, several unusual aspects to this case. To my knowledge there has been no report of a case of acute porphyria associated with the hemorrhagic phenomena observed here. The occurrence of numerous retinal hemorrhages and bilateral oculomotor nerve palsy with rapid recovery can only be explained on a hemorrhagic basis. The porphyrins are unassociated with the synthesis or the destruction of red cells; consequently the urinary porphyrins cannot be attributed to the bleeding.

The abdominal pain, associated with intense constipation as a presenting complaint followed by mental confusion, represents a very typical onset. The skin lesions were characteristic. The finding of porphyrins in the urine clinches the diagnosis. Hematoporphyria need not necessarily be present.

Summary

A case of acute porphyria associated with retinal hemorrhages and bilateral oculomotor nerve palsy is presented.

309 Sterling Place.

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SOCIETY PROCEEDINGS

Edited by DONALD J. LYLE, M.D.

NEW YORK SOCIETY FOR CLINICAL OPHTHALMOLOGY

March 7, 1949

DR. BENJAMIN ESTERMAN, *president*

RETINAL TEAR WITHOUT DETACHMENT

DR. FRANK H. GRAUPNER presented the case of the month, a 58-year-old man who saw a veil over his left eye after lifting a heavy load and bending down. He was seen a few hours later and a vitreous hemorrhage which reduced the vision to 20/100 was observed. In the extreme nasal periphery at the 9-o'clock position was a tongue-shaped retinal tear about the size of a disc.

After eight days the vitreous had cleared sufficiently to observe a retinal flap hanging down into the vitreous, about five disc diopters in size, best seen with a +8.0D. lens. From the 10- to 12-o'clock positions, a semicircular, fine, whitish line could be seen which represented the margin of the retina from which the flap was torn off. This line in its entire length was tightly attached to the underlying tissue and was nowhere curled in. Two vessels ended abruptly at the edge of the retina. The myopic pattern of the fundus was the same above and below this line of demarcation, the retina being transparent. Only the whitish line suggested the edge of the retinal tear.

All over the extreme periphery of the eye, degenerative changes were conspicuous. Because of this extensive damage an electrocoagulation was done to the affected area, with the ball electrode. The upper large flap became reattached, even without the globe being perforated. The vision was 20/30 at discharge.

Dr. Graupner discussed several outstanding features of this case. First, the vitreous hemorrhage; for, as Knapp pointed out in his series, three cases out of five have vitreous hemorrhages in the beginning, as in this case. Vitreous hemorrhages would seem to be more frequent in cases of retinal tears without detachment than in ordinary detachments, and it is usually the hemorrhage which brings the patient to an ophthalmologist.

The second point of interest in this case was that no detachment followed the large multiple retinal tears. Arruga suggested that choroiditic changes make the retina adherent and thus prevent the escape of fluid underneath the retina. As Knapp pointed out, in three of his cases, no choroidal lesions could be seen ophthalmoscopically. In the case presented there were no signs of choroiditis along the long margin of the retinal tears. A possible explanation was that a separation took place in the inner retinal layers.

Vogt underlined the findings of Hanssen that Henle's layers is the most frequent place of cystoid degeneration. He observed a splitting of the retina in 2 or 3 layers, but found this only in the periphery and in small holes. The smoothly attached margin of the retina in this case suggests that at least the external limiting membrane still covered the area where the large flap was torn off, thus preventing the fluid from separating the retina from the pigment epithelium underneath.

In this case a cystoid degeneration of the retina in the form of fine vacuoles can still be seen close to the tear near the equator of the globe. Frequent vitreous hemorrhages in such cases could be explained by the fact that the inner retinal layers carry more blood than the external.

Discussion. Dr. Ludwig von Sallmann said that the size, shape, and number of tears in Dr. Graupner's patient accentuate

the enigmatic nature of the condition, which was the subject of controversy years before Gonin expressed his ideas on the pathogenesis of retinal detachment. Later, the occasional occurrence of horseshoe tears without subsequent detachment was the most valuable argument against Gonin's theory which is now accepted almost everywhere.

In attempts to explain the unusual course one turned to forces of traction and negative pressure from the vitreous space and to forces of adhesion and negative pressure present in the potential subretinal space.

Although negative pressure may contribute essentially more to the final analysis of the condition, Dr. von Sallmann said that he would like to mention two other mechanisms, one of which was discussed by Dr. Graupner.

Studies on the vitreous retinal system convinced Gonin and Lindner that first adhesions between retina and vitreous and then detachment and shrinkage of the vitreous are the usual prerequisites of typical horseshoe tears. In Dr. Graupner's patient and in an analogous patient of Dr. LeGrand Hardy seen three years ago the vitreous was detached far forward. In neither of these eyes was it possible to examine biomicroscopically the lesions in the retina because of their peripheral location. However, in Dr. Hardy's patient, a free operculum lying far in front of the retina indicated that the vitreous had lost contact with the region of the tear. The apronlike appearance of the retinal flap in Dr. Graupner's patient suggested a similar behavior of the vitreous. The question could be raised, therefore, whether such disengagement of the vitreous from the flap and the adjacent retinal tissue could have something to do with the favorable course.

Dr. Graupner mentioned the possibility of a retinal factor, that is, splitting of the retina, a retinal schisis. When Dr. von Sallmann first saw the patient he had the impression that the retina was flat, detached adjacent to the temporal tear, but this observation was not unequivocal enough to serve as an argument against the splitting theory. On the contrary, such a mechanism deserves full consideration despite the fact that no histologic evidence is available for such a condition and despite the fact that cystic changes in the periphery of the fundus of Dr. Graupner's patient were by no means excessive. Unfortunately it is not possible to apply the differential diagnostic signs to distinguish between complete and partial holes in the macula and peripheral retinal tears.

Dr. von Sallmann said that he wondered whether Dr. Graupner agreed with him that it is safer for the time being to adhere to the classical interpretation, which goes back to Gonin and Lindner, that is, that the inflammation which causes the vitreous-retinal adhesions may have also caused minimal chorioretinal synechias. In Graupner's and Hardy's, as in several cases of Arnold Knapp, they could have been so fine that they were not seen ophthalmoscopically. Gonin has described histologically such choroiditic changes.

As to treatment, Dr. von Sallmann referred to Dr. Dunnington's observation that a retinal tear without detachment was followed by retinal separation several months after onset. Second, he referred to a patient of Dr. Lindner who had typical retinal tears in both eyes. One eye developed retinal detachment and was successfully operated. The patient did not consent to an operation on the second eye and no retinal detachment developed in this eye. Dr. von Sallmann concluded that it is obvious that one cannot prognosticate what is going to happen so that cautious surgery, as described by Graupner, seems to be the treatment of choice.

Dr. Charles A. Perera said that he saw the patient four days after the reported onset of the condition. The appearance was not typical of those cases described as hole in the retina without detachment and was complicated by hemorrhage. Dr. Perera said

he thought the patient had a flat detachment adjacent to the hole. He then reviewed the various causes of retinal holes and said that, in the case presented, the explosive force of the hemorrhage was the probable cause. He said that he had seen six cases of retinal holes and the end results varied. He advised surface diathermy as the best surgical procedure in most cases.

Cataract extraction

Dr. Ray K. Daily, Houston, Texas, presented (by invitation) a motion picture on this subject.

Laceration of the canaliculus

Dr. Benjamin Esterman presented six cases of fresh lid laceration involving the canaliculus, in which the usual method of repair was modified. The former method of using a metal sound to splint the canaliculus was found to interfere with proper suturing of the conjunctival aspect of the wound and to render unsafe the use of a pressure dressing postoperatively for fear of necrosis caused by pressure of the metal.

Instead, a No. 2 catgut suture on a half-curve atraumatic, noncutting needle is threaded through two sections of the lacerated canaliculus, into the lacrimal sac, and out through the anterior sac wall and skin. Prior to its passage, the point of the needle is blunted ever so slightly by passing it once over the surface of a whetstone to prevent the point from catching the mucosa of the canaliculus and sac and lacerating it.

In all six cases, complete patency of the lumen of the canaliculus was achieved, during follow-up periods of from 1 to 3 years. This was shown by (1) absence of tearing, (2) ease of irrigation of the injured duct during the follow-up period, and (3) evacuation time of fluorescein solution from the conjunctival sac of the injured eye as compared with that of the other eye.

Dr. Esterman concluded by emphasizing two factors: (1) That all cases were operated within 12 hours from the time of the injury and (2) that the torn edges of the canaliculus were found with surprising ease even in very ragged lacerations.

Congenital and acquired dacryocystitis

Dr. Ralph O. Rychener, Memphis, Tennessee, said (by invitation) that, in the small field of lacrimal disease, several noteworthy changes in treatment have been observed in recent years. In congenital stenosis, it was formerly advised either to give no treatment at all or to pass giant Ziegler probes after slitting the upper punctum; the modern concept is to pass tiny, No. 0 or No. 00 Bowman probes in the first few weeks or months, with the result that 1 or 2 treatments cure a condition which by delay may result in acute dacryocystitis with all its complications, including osteomyelitis of the maxilla.

Epiphora used to be managed by slitting the canaliculus even though a real constriction of the lacrimal duct could be demonstrated, with the result that tearing always persisted after the real pathologic condition in the duct was corrected. Lacrimation due to hypersecretion is now attacked at its source, either by X-ray therapy directed at the gland to diminish its output, or by cocainization or alcohol injection of the sphenopalatine ganglion to obstruct the nerve supply to the gland, since the tears are frequently increased by irritating lesions in the nose. Epiphora due to senile ectropion requires correction by one of the accepted treatments of lid shortening, but when it is due to outward displacement of the lower punctum only, a few well-placed Ziegler cautery punctures will yield a most satisfactory result.

Hyposecretion as evidenced by keratitis sicca is well managed by closure of the puncta with the actual cautery, whereupon the mucous glands of Krause furnish enough lubrication to keep the cornea moist and comfortable. It is well to seal off only the lower punctum at first as lacrimation may be sufficient to cause tears to stand

constantly in the eyes if too enthusiastic treatment is employed. The upper punctum can always be closed at a later date if necessary.

Dr. Rychener said that, as a resident on a fine ophthalmic service, he was taught no surgical procedure on the lacrimal sac other than excision, which of course never cured chronic dacryocystitis, as the canaliculi still remained to act as potential sources of infection for the debilitated cornea. Dacryorhinostomy of one form or another has been the greatest advance in this field in the past 25 years and there exists no longer any excuse for any other procedure, provided the passageway from the punctum to the sac is intact. The evidence of any mucocele, no matter how small, in the lacrimal sac is an indication for such therapy, and one should not hesitate even though only one, and that an upper, canaliculus is intact.

Because of its good results in his experience, Dr. Rychener said he prefers the Dupuy-Dutemps dacryorhinostomy as modified by Chandler, which provides a three-sided tunnel of mucous membrane which is less likely to be occluded by bony ingrowth. All ethmoidal cells which happen to be in the way should be completely exenterated and care should be taken not to close the mucous membrane of the lacrimal sac with that lining an ethmoidal cell. A large bony window, at least 10 by 12 mm. or preferably more, is desirable as it facilitates the handling of the flaps. Special atraumatic sutures and a small mosquito hemostat as a needle holder are refinements which have been found valuable and time saving. This operation has been used on patients from 18 months to 72 years with complete satisfaction.

Bernard Kronenberg,
Recording Secretary.

OPHTHALMOLOGICAL SOCIETY OF MADRID

February 18, 1949

Palpebral ptosis

Dr. Marin Amat discussed the superiority of the Motais operation in the treatment of palpebral ptosis, covering extensively every phase of the subject—the etiology, clinical forms, patient's age and social status, and so forth. In classifying the etiology, he divided the cases into two large groups, the congenital and the acquired. In both of these there are two varieties according as to whether the paralysis stems from the cranial nerve (a branch of the motor oculi) or from the sympathicus.

The principal part of the paper was devoted to treatment which must take account of the etiology, whether the condition is congenital or acquired and especially whether it is an isolated phenomenon or part of a complex clinical picture. Surgical intervention is indicated only when the condition is isolated. One must also watch the extent of the affection, whether it is partial or total, in order to choose the best operative procedure. These he divided into five groups: (1) Procedures which excise a portion of the tissues of the upper lid; (2) procedures which advance the tendon of the levator muscle; (3) procedures which substitute the frontalis muscle for the levator muscle; (4) procedures which utilize the superior rectus muscles; and (5) mixed procedures. The author advocates the Motais operation of substituting the superior rectus for the levator. This operation, with his modifications, gives the best functional results.

Discussion. Dr. Mario Esteban said that the innumerable operations for ptosis can be classified into three groups:

1. Those which shorten the lid. They should be avoided as they may produce a lagophthalmos which is even worse than the ptosis.

2. Those which shorten or advance the levator muscle. These are especially indicated in cases of ptosis due to insufficiency or relaxation of the levator.

3. Those which aim to substitute the occipito-frontalis or the superior rectus for the levator. These should be preferred for cases of ptosis due to paralysis of the levator. Naturally they are indicated only when there is an isolated paralysis of the levator muscle. One must make sure that there is not a complete paralysis of the third nerve, in which case the operation would reveal a diplopia hidden by the drooping lid and correcting the ptosis would make matters worse.

Supplanting the levator with the frontalis (Hess method) is an easy operation to perform, but its effect is to move the lid only in a vertical direction which is not exactly normal nor correct. Supplanting the levator with the superior rectus (Motais operation) follows most perfectly anatomic and physiologic principles, since both muscles pull in the same direction, are innervated by the same nerve, and are synergists.

Working on the same principles as Motais, we developed a technique which we believe is better. Instead of taking a flap from the superior rectus to attach to the tarsus, we suture the whole levator to the whole superior rectus, more posteriorly the more marked the ptosis. The prime advantage of this method is that traction on the lid is not limited to one point, but is accomplished by means of all the insertions of the levator, with its cutaneous and tarsal tendons extending fan-shaped along the width of the lid.

Dr. B. Carreras Duran: The result of Dr. Marin Amat's operation by the Motais method is very satisfactory. It is worth noting that the first Motais operation in Spain was published by Professor Marquez. It was a case of unilateral ptosis. The second case was published by me in 1918. This was a case of bilateral ptosis with excellent results. In spite of this, however, I believe that the procedure outlined by Dr. Mario Esteban is more logical, since the original tendon of the levator is acted on by the superior rectus. The innervation of the levator and of the superior rectus stems from a filament which divides into two branches, one for each muscle. In reality, however, the innervation of each of these muscles comes from a different group of cells in the nucleus of the motor oculi.

Dr. B. Carreras Matas: In choosing an operation for ptosis, one must take into account that, if the patient does not have any wrinkles in his forehead, an operation to utilize the frontalis muscle should not be made. One must choose the Motais operation.

Dr. Marin-Amat (in reply): Dr. Mario Esteban's method of anastomosing the tendons of the levator to the superior rectus, which may be called Motais operation in reverse, presents serious difficulties in its execution and offers little or no guaranty of its practical efficiency since it is difficult to judge the pull of the levator tendon in its new position, something which is easy in the Motais operation. As for anastomosing the whole tendon of the levator to the superior rectus, this is impossible because the levator has a width of some 35 mm. and the superior rectus, approximately 12 mm.

Although dissociation on closing the lids and elevating the eyeball during sleep is a function acquired during the earliest time of life, it can be acquired in later life by training, as in all our cases.

The objections of Dr. Carreras Duran have been answered in the reply given to Dr. Mario Esteban. The question of the innervation of the levator and the superior rectus, has not yet been settled. According to Bernheimer, each muscle has its own nucleus; according to Hensen and Volckers, the levator and the superior rectus have a common nucleus. However, this is rather far removed from our subject of the surgical treatment of ptosis. The surgeon may not be able to obtain physiologic perfection in

his operations, but he must try to approach it.

Spurious retrobulbar neuritis

Dr. Carreras Matas said that the appearance of homonymous hemianopia threw doubt on the diagnosis of retrobulbar neuritis in a patient who had shown a central unilateral scotoma. Further exploration gave evidence of a chromophobic adenoma of the hypophysis. After treatment with X rays the scotoma disappeared, the visual fields were normal, and the patient recovered normal visual acuity.

Discussion. Dr. Mario Esteban: This interesting case, so well handled by Dr. Carreras Matas, carries many lessons. As to the clinical diagnosis, repeated examination of the visual fields led to the discovery of a hemianopia, where previously there seemed to be only a simple retrobulbar neuritis. With reference to the topographical diagnosis: A hypophyseal tumor does not always affect the chiasma symmetrically, producing bitemporal hemianopia. The tumor may grow eccentrically, or vascular compression may cause a hypophyseal tumor to rebound to one side and involve one optic tract, producing a defect corresponding to homonymous hemianopia.

Visual-field tests show clearly that the X-ray therapy caused the tumor to regress. In a tumor of the hypophysis, the ophthalmologist has to refer the patient to a radiologist or to a brain surgeon. In spite of the marvelous progress of cranial surgery, we must remember the seriousness of such heroic interventions. However, we must also remember that many times radiotherapy fails and the case is brought to the surgeon after a delay, making the operation more difficult and the outcome less likely to be successful. We may begin with radiotherapy and diligently watch the consequences of the treatment. A favorable result, as in this case, will lead us to continue the same treatment. But if this treatment proves ineffectual, then the patient must be sent immediately to the brain surgeon. Any loss of time will lessen the possibilities of a surgical cure.

Joseph I. Pascal,
Translator.

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NEW EVIDENCE RELATING TO PROPRIOCEPTIVE SENSE IN THE EXTRINSIC EYE MUSCLES

Muscles spindles have, for the first time, been definitely demonstrated in the extraocular muscles of man by Sybil Cooper and Peter M. Daniel. The methods used and the results obtained are reported in *Brain* for March, 1949.

At the 1949 meeting of the Western Section of the Association for Research in Ophthalmology, Flanagan, Hill, and Kvernland reported electrophysiologic experiments conducted in Dr. Kenneth Swan's department at the University of Oregon. They demonstrated no constant barrage of postural reflexes in the extraocular muscles during the resting (static) state of the muscle.

Sherrington so convincingly showed the dependence of posture, and presumably tone, upon proprioceptive reflexes that, as a result of his work, proprioceptive sense has been thought by many physiologists to play an important part in orienting and modifying

certain visual perceptions, as projection, stereopsis, and interpretation of motion on the retina. Older authorities, as Helmholtz, Tscherning, and Hering, attributed no importance to the influence of proprioception from the eye muscles in these visual perceptions.

In 1936, Ludvigh and I investigated proprioceptive sense in the extraocular muscles. We could find no striking histologic evidence in favor of it, as up to that time muscle spindles had not been found in human extrinsic eye muscles, and we could not demonstrate position sense derived from sensory impressions from the extraocular muscles, and therefore concluded that "proprioceptive sense, if extant in the extraocular muscles, plays no role in projection, stereopsis, and the interpretation of motion on the retina."

In 1939, Chavasse, in his textbook, *Worth's Squint*, answered some of our arguments against the existence of proprioceptive sense with the hypothesis that proprioceptive sense is readily inhibited if the proprioceptions are bizarre and incapable of synthesis with other perceptions. He goes on to state that "the immediate, indeed instantaneous, development of this inhibition of proprioception accords in the first place with the vagueness of ocular proprioception in general, unless reinforced by alliance with exteroceptive stimuli."

The recent article by Cooper and Daniel is important because of the evidence it contains of proprioceptive end-organs in the eye muscles. These authors studied the orbital contents removed at necropsy from about 60 patients.

Serial sections were made so that the total number of muscles spindles present in a particular muscle could be counted and their exact distribution throughout the muscle ascertained. The extrinsic eye muscles of various animals were examined in a similar manner. The authors found the muscle spindles in the extrinsic eye muscles to be smaller and more delicate end-organs than comparable structures in other somatic muscles.

Like its larger counterpart, the spindle in the eye muscle consists of a group of fine cross-striated muscle fibers with a rich nerve supply enclosed in a torpedo-shaped capsule of fibrous tissue. This capsule is very much thinner in the eye muscle spindles than in muscle spindles of other human somatic muscles, and the considerable quantity of connective tissue around the muscle fibers of the eye muscles has prevented the recognition of these capsules particularly if any autolysis has taken place prior to fixation of the tissue.

This difficulty, along with the location of the spindles at the ends of the muscles and their absence in the belly of the muscle, explains in part the failure of earlier investigators to find them.

Approximately 47 muscle spindles were counted in one inferior rectus muscle. Inferior recti oculi always appeared to contain the greatest number of spindles although all the recti were richly supplied. The obliques seemed to have a rather smaller complement than the recti. The levator palpebrae superioris was always poorly supplied with spindles.

For comparison with the extrinsic eye muscles the distribution and number of spindles in the first lumbrical muscle of the human hand was studied. This muscle is about the same length as the rectus oculi muscle and is supposed to be one of the most finely adjusted of all the somatic muscles. The spindles in the lumbrical muscle were present throughout the muscle, being most common in the belly. They were strikingly apparent owing to the thickness of their capsules. The total number of spindles found in the human first lumbrical muscle was 49.

Up to the present time Cooper and Daniel have found muscle spindles in the extrinsic eye muscles of the cow, gnu, goat, wild and domestic sheep, pig, giraffe, and chimpanzee, and have found no muscle spindles in the

extrinsic eye muscles of the rabbit, cheetah, cat, dog, bear, or macaque monkey.

They remarked on the incongruity of these findings, noting that spindles were found in animals that tend to move their eyes and have highly developed visuomotor reflexes, and absent in those animals whose eyes are relatively fixed and who rely on movement of the head for change in direction of gaze, with little range of eye movement. To quote directly:

"It is clear from the evidence presented in this paper that muscle spindles, the recognized sensory endings for the prioceptive sense in somatic muscles, are present in all human extrinsic eye muscles and in the eye muscles of certain animals. Their function in these muscles must surely be similar to their function in other somatic muscles. They provide a tangible proof of sensory endings in the extrinsic eye muscles and they give to these muscles a means of recording their own activity."

The new evidence presented by Flanagan, Hill, and Kvernland as well as that by Cooper and Daniel must be incorporated into our concept of the physiology of the extraocular muscles. Muscle spindles in other somatic muscles are known to be proprioceptive organs and demonstration of them in the eye muscles suggests that they serve a similar sensory function here. The importance of stretch reflexes as subserved by "proprioceptive sense" in the role of establishing postural tone must be evaluated in the light of the evidence presented by Flanagan and others.

It is quite possible that the extraocular muscles have an elastic resiliency independent of afferent-efferent impulses derived from myotatic reflexes. This resiliency permits smooth coördinated movement and lessens the necessity of a concept of reciprocal innervation leading to active relaxation of the antagonist muscle. Furthermore, the eye has the retina, a sensory organ "par excellence," to guide and control its movements, and no one can question the importance of retinoception in preventing ataxic movements of the eye.

After consideration of the evidence, it seems that the proprioceptive sense of the eye muscles might be relegated to a vague orienting of the position of the eyes to the position of the head, with, as Chavasse suggested, an increasingly greater effect as it is reinforced by other reflexes. The role it may play in influencing visual perceptions is enhanced by the new histologic evidence of proprioceptive end-organs in these muscles.

S. Rodman Irvine.

THE LOS ANGELES MIDWINTER POSTGRADUATE COURSE

The 19th annual midwinter postgraduate course of the Los Angeles Research Study Club was held from January 15th to 27th, the week of the 15th to the 21st being devoted to ophthalmology. Dr. Conrad Berens and Dr. Raymond Meek of New York were the principal speakers. Their lectures covered the various phases of surgery, ocular fatigue and asthenopia, reading disability, surgical anatomy, and therapeutics. Dr. Frederick C. Cordes discussed the congenital and acquired anomalies of the optic disc.

Instruction courses were given by Dr. A. E. Cruthirds, Dr. S. Rodman Irvine, Dr. Raymond Meek, Dr. Harold Whalman, and Dr. Frederick C. Cordes.

The course was well attended, the 289 registrants representing 24 states, Canada, and the Hawaiian Islands.

On Tuesday night Dr. Phillips Thygeson delivered the third Estelle Doheny Eye Lecture, his subject being "The etiology and treatment of phlyctenular keratitis."

The round-table luncheons were very popular, those attending the course putting many questions to the instructors on subjects that they had discussed.

Many men attend this course every year and the good fellowship, renewal of friendships, and exchange of ideas is one of the

outstanding features of the course. In addition, those in charge see to it that the social side is well taken care of. There is a reception on the first day, an organ recital, a cocktail party, a theater party, and tickets are available to practically all of the nationally known radio broadcasts which originate in Hollywood. "Holiday Dream" added a good deal to the writer's enjoyment at the course by winning the eighth race at Santa Anita.

Another noteworthy feature of this course is that those in authority have used the profits from the course to further research. Among the institutions that have received sizeable grants for research in ophthalmology are the University of Iowa, the University of Oregon, and the University of California. At this year's meeting there was presented to the Incorporated Committee of the Research Study Club a report of an outstanding piece of research on toxoplasmosis carried on under one of these grants. This report will be published soon.

In addition to such internationally known men as Bielschowsky, Elschnig, Wright, and others, the Research Study Club has brought many nationally known ophthalmologists to the West Coast. The midwinter postgraduate course of the Research Study Club has become one of the ophthalmic traditions of the West.

Frederick C. Cordes.

OBITUARY

PLINIO H. MONTALVÁN
(1905-1950)

On the morning of January 18th, Dr. Plinio H. Montalván died in Havana of a heart attack. He was 45 years of age.

Born in 1905 at Cienfuegos, Cuba, Dr. Montalván studied at the University of Havana from which he was graduated in 1927. In 1930, he studied at the School of Aviation Medicine, Randolph Field, San Antonio, Texas, from which he was graduated as flight surgeon. After this, he spent two years at the Wilmer Ophthalmological Institute of The Johns Hopkins University and Hospital. He was a devoted disciple of Dr. Wilmer whom he followed to Washington.

Dr. Montalván was a member of the Cuban Opthalmological Society and belonged to the medical staff of the Cuban Army. He had the highest esteem of his colleagues and was, at the time of his death, on the staff of the Miramar Hospital and a member of the Asociación Cubana de Beneficencia.

Besides his wife, Mrs. Ruth Warner Montalván, Dr. Montalván leaves two small sons and a daughter.

Tomás R. Yanes.

BOOK REVIEWS

VISION: ITS DEVELOPMENT IN INFANT AND CHILD. By Arnold Gesell, M.D., Frances L. Ilg, M.D., and Glenna Bullis (assisted by Vivienne Ilg, O.D., and G. N. Getman, O.D.). New York, Paul B. Hoeber, Inc., 1949. Clothbound, 352 pages, 179 illustrations. Price $6.50.

The first group of chapters in this book will be of great interest to the ophthalmologist as they represent expert studies in the field of development of the infant and young child. The relationship of vision to this physical and mental expansion of the personality will be new to most ophthalmologists. Furthermore, these sections would be valuable for any intelligent parents. A knowledge of their contents would enable them to understand much more clearly the purpose of the child's actions and give insight into the motivating processes as growth takes place. These chapters would also serve as yardsticks for expectations and indicate to ophthalmologists and parents when these processes are delayed or abnormal.

As one reaches the middle of the book, there are introduced experiments with

retinoscopy which leave the ophthalmologist with a feeling that there has been an attempt to draw conclusions from this special test that are decidedly questionable. Retinoscopy is performed with undilated pupils, the child fixing on a distant object, and the observer also being at a considerable distance from the child. Attempt is made to deduce the nature of the child's reaction from such things as observations of the "with" or "against" movements and color changes, such as brightness, dullness, and whiteness of the reflex.

The reader immediately wonders why the alleged changes were not checked under cycloplegia which would have eliminated the possibility that the accommodative effort in the child was important in the changes described. The authors state that they thought the conditions were much more natural without cycloplegia and gave this as the reason for not using this obvious method which would have eliminated one of the disturbing factors. It is true that the reflex can be obtained after a little practice through the dilated pupil at a 20-foot distance. But to attribute these alleged color changes to mental processes impresses the reviewer as extremely doubtful.

However, the idea is new and anything new should be given thoughtful consideration with careful checks. The obvious procedure would be checking with cycloplegia. The serious doubt of the conclusions of the retinoscopists tends to shake the confidence in some of the later material in the book. This is unfortunate since certainly the writers get off to a fine start in unravelling the relationship of the development of the eye to the body as a whole. But one can scarcely believe that the conclusions from retinoscopy which are stressed have the significance attributed to them by the authors. Lawrence T. Post.

GOETHE AS A SCIENTIST. By Rudolf Magnus. (Translated by Heinz Norden.) New York, Henry Schuman, Inc., 1949. 250 pages with bibliography and index. Price, $3.50.

This interpretative work, originally published in 1906 as *Goethe als Naturforscher*, is now available in an excellent English version thanks to the interest created by the Goethe bicentennial. The book covers in lucid detail the scientific aspect of Goethe's personality and describes fully his experiments and discoveries in the fields of comparative anatomy, morphology, light, and color.

Goethe amassed a vast array of color data, and the optical instruments with which he conducted his ingenious experiments are still preserved in the Goethe House. His viewpoint was solely subjective. Even after studying Kant he never realized the importance of distinguishing sharply between his sensations and the stimuli that aroused them. Nor did he apparently apply to his own work his belief that "it is in the transition from fact to judgment that the scientist exposes himself to the greatest danger of error."

Goethe, as a many-sided creative artist, has been aptly compared to Leonardo da Vinci. Goethe sought unity everywhere in nature, and Magnus correctly stresses the influence of this leitmotif in all his work. The book deserves, and should win, a wide audience. James E. Lebensohn.

THE VALUE OF HORMONES IN GENERAL PRACTICE. By W. N. Kemp. Minneapolis, Minn., Burgess, 1949. 115 pages. Price, not listed.

This mimeographed, spiral-bound book of 115 pages systematically tells all that the general practitioner is likely to need to know about each of the endocrine organs. From the point of view of the endocrinologist, the ophthalmologist is a general practitioner and the book is to be highly recommended to him. The arrangement is perspicuous, nonessentials are omitted, and matters of importance are adequately described.

Despite its schematic arrangement, the book is in no sense a mere outline. The function and diseases of each gland, the syndromes that are associated with it, the means of differential diagnosis of the latter, and the pharmaceutic preparations for each gland are exhibited in detail.

There are references for further reading, though it is not likely that the ophthalmologist will fail to find all he needs in this text. There is also a table of normal values for the chemical analysis of blood that are of interest in endocrine disturbance.

F. H. Haessler.

TRANSACTIONS OF THE OPHTHALMOLOGICAL SOCIETY OF THE UNITED KINGDOM. London, J. and A. Churchill, Ltd., 1947, Volume 67, 530 pages.

This volume contains the reports of the eight affiliated ophthalmologic societies of the United Kingdom.

The presidential address by A. J. Ballantyne was a brief summary of the aging of the eye and the associated physical and mental signs of senescence. The immense resources going to waste in the valuable experience and unused skills of the elderly men and women were noted. The importance of patience and long views in political argument and reform was suggested.

Rhinology in relation to ophthalmology was discussed by Marshall, Howells, Melanowski, and Godtfredsen.

Diseases affecting the retinal veins and the associated variation in caliber, sheathing, capillary circulation evidenced by microaneurysms, hemorrhages, exudates, or "new vessel" formation were beautifully demonstrated by Ballantyne and Michaelson.

Ida Mann records experiments showing the induction of cancer of the lens of mice using pure live strains of mice and chemical carcinogens. The ability of the lens epithelium to become malignant has been demonstrated.

The Doyne Memorial Lecture was given at the Oxford Ophthalmological Congress by Dr. Leon Stone of Yale University on the "Return of vision and functional polarization of the retina of transplanted eyes." Salamander eyes were used in this study. Vision can return four times in the adult salamander eye repeatedly transplanted to a new host. The methods of demonstrating restored vision and retinal orientation were conclusive.

The trying problem of "The contracted socket" was presented by T. Pomfret Kilner and H. B. Stallard. The mechanical problem existing, the use of Thiersch grafts, acrylic molds, and the ultimate prosthesis required were discussed in considerable detail.

George W. Black, in the treatment of retinal detachment, has used methylene blue (0.18 cc. of 0.1-percent strength) injected into the subretinal space. The area of detachment stains rapidly, the choroid does not stain, tears are visible as red patches in contrast to the blue-stained area of detachment. Atrophic areas, not normally visible, are unstained. This technique may be of real assistance. Black has also obtained a notable reduction in the capacity of the eyeball by the surface application of the diathermy electrode over a selected scleral area. The eyeball is first collapsed by the evacuation of fluid through a scleral trephination. A marked scleral flattening is obtained.

J. P. F. Lloyd using the title "Making perimetry pay" outlines the technique, interpretations, and pitfalls of clinical perimetry.

Norman Cutler gave an interesting demonstration of the ball-and-ring implantation for use in enucleation.

Throughout the volume are many instructive clinical case reports.

William M. James.

ABSTRACT DEPARTMENT

EDITED BY DR. F. HERBERT HAESSLER

Abstracts are classified under the divisions listed below. It must be remembered that any given paper may belong to several divisions of ophthalmology, although here it is mentioned only in one. Not all of the headings will necessarily be found in any one issue of the Journal.

CLASSIFICATION

1. Anatomy, embryology, and comparative ophthalmology
2. General pathology, bacteriology, immunology
3. Vegetative physiology, biochemistry, pharmacology, toxicology
4. Physiologic optics, refraction, color vision
5. Diagnosis and therapy
6. Ocular motility
7. Conjunctiva, cornea, sclera
8. Uvea, sympathetic disease, aqueous
9. Glaucoma and ocular tension
10. Crystalline lens
11. Retina and vitreous
12. Optic nerve and chiasm
13. Neuro-ophthalmology
14. Eyeball, orbit, sinuses
15. Eyelids, lacrimal apparatus
16. Tumors
17. Injuries
18. Systemic disease and parasites
19. Congenital deformities, heredity
20. Hygiene, sociology, education, and history

1

ANATOMY, EMBRYOLOGY, AND COMPARATIVE OPHTHALMOLOGY

Ochoterena, Isaac. **Eye of Tapayaxin, Phrynosoma orbiculare Wiegmann.** An. Soc. mex. de oftal. **23**:80-94, April-June, 1949.

With excellent photomicrographs, the author presents his study of the ocular structure of this small Mexican reptile. (9 figures.) W. H. Crisp.

2

GENERAL PATHOLOGY, BACTERIOLOGY, IMMUNOLOGY

Belmonte Gonzales, Nicolas. **Experimental anoxia of the retina.** Arch. Soc. oftal. hispano-am. **9**:710-714, July, 1949.

To support his contention that anoxia is the important factor in the pathogenesis of retinopathies, Belmonte produced retinal anoxia experimentally in dogs by creating a general hypertension. He partially tied both renal arteries and produced an anemic anoxia by repeated bleeding. In some cases the centrifuged plasma was reinjected into the animal. The ophthalmoscopic picture in the hypertensive and anemic dogs was characterized by pale dilated veins, narrow arteries and disappearance of the fine branches but there was no hemorrhage or edema. The eye of one dog was enucleated ten days after the bleeding. There was a diminution of the ganglion cells of the retina, in many of the cells the protoplasm had a homogenous appearance, as in degeneration, and there was an increase of microglial tissue. Ray K. Daily.

Kaiser, M. **Animal eye as aid in virus research.** Wien. klin. Wchnschr. **61**:696-698, Oct. 21, 1949.

The cornea of the animal eye is particularly suitable for the development of virus elements, because of the very simple structure of this tissue, its transparency and the absence of vessels. Scarification of the cocainized cornea is carried out with a suitable instrument and the diluted virus preparation is then rubbed into the cornea. Another method is inoculation of the aqueous and it is also possible to introduce the virus by cannula puncture through the sclera directly into the vitreous body. The intraocular inoculation with rabies virus is considered as valuable as intracranial inoculation.

The animal eye is the only medium for

experiments with virus diseases of the human eye. Only monkeys showed a certain susceptibility to the trachoma virus.
Theodore M. Shapira.

Sysi, R. **Histo-pathological studies of the blood-vessels of the eye.** Brit. J. Ophth. **33**:739-754, Dec., 1949.

The author studied histologically 408 eyes from corpses. It was found that the blood-vessels of the eye are subject to the same pathologic changes as occur elsewhere in the body. The changes in the control material are slight, and occur after the age of 30 years, mainly in the outermost parts of the blood vessels, and take the form of adventitial and medial thickening, with slight fibrosis and sometimes homogenization, fatty changes, and, rarely, slight thickening of the intima, except in the smallest vessels.

In arteriosclerosis the changes are usually more obvious, though some cases do not differ from those in the control group. The changes found in arteriosclerosis generally occur in the whole wall and are obvious in the media and intima. After arteriosclerosis develops there is marked proliferation of the elastica, and delamination. Later there is complete hyaline degeneration and also obstruction. Atheromatous foci occurred in one case. The changes in nephrosclerosis do not differ essentially from those in arteriosclerosis, but are more easily discernible. There is an increase in the severity of the vascular changes in the retina, and even more so in the choroid. Nephritic cases have, in addition, edema in the vascular wall which differentiates them from essential hypertension. Arteriosclerotic changes are relatively frequent in the blood vessels of the nephritic group.

The changes in all groups first involve the arterioles of the optic nerve and the posterior ciliary arteries, and afterwards the blood vessels of the choroid. Changes are rare in the arterioles of the retina and its central artery. These are not demonstrable until severe arteriosclerosis develops. Both retinal and choroidal changes first occur posteriorly, but extend to the ora serrata. Changes are less frequent in the vessels of the ciliary body than elsewhere in the vascular system of the eye, and in the iris least of all. The extent of the changes is greatest where they appear earliest. The amount varies in the same and different areas. There is one exception to this; in subjects with marked sclerosis, nephrosclerosis and nephritis the changes in the retina are noticeably greater than elsewhere. The retinal vessels tend to reflect the condition of the kidneys, but not the condition of the cerebral blood vessels. There is no marked disparity between the blood vessels of the left and the right eye. (8 photomicrographs, 4 charts.) Orwyn H. Ellis.

3

VEGETATIVE PHYSIOLOGY, BIOCHEMISTRY, PHARMACOLOGY, TOXICOLOGY

Auricchio, G. **Complicated cataract. 1: The pathogenesis of complicated cataract secondary to iridocyclitis.** Ann. di ottal. e clin. ocul. **75**:89-99, March, 1949.

Studying induced tuberculous iridocyclitis in rabbits, Auricchio found diminution in the glucose content of the aqueous and the lens, increase in the lactic acid content of the lens, an initial increase and a subsequent decrease in the permeability of the lens capsule, and diminished consumption of glucose by the lens fibers.
Harry K. Messenger.

Corrado, Mario. **The relation between the histamine of the aqueous humor and that of the cerebrospinal fluid, and their importance from the physiopathologic and clinical point of view.** Ann. di ottal. e clin. ocul. **75**:33-44, Feb., 1949.

Using a quantitative biologic method, Corrado found that the concentration of

histamine in the aqueous humor (0.055 gamma per cc.) is higher than that in the cerebrospinal fluid (0.025 gamma per cc.). The existence of a blood-cerebrospinal barrier for histamine has already been established, and Corrado believes that a similar blood-aqueous barrier exists. The study of histamine concentration may be useful in determining the allergic nature of certain ocular diseases.

Harry K. Messenger.

Duke-Elder, Stewart. **The physiology of the intraocular fluids and its clinical significance.** Tr. Am. Acad. Ophth. pp. 18-25, Sept.-Oct., 1949.

Both physical and chemical processes, filtration and secretion, are involved in aqueous formation. The role of each differs quantitatively and qualitatively in the anterior and posterior ocular segments. The capillary walls are freely permeable to water, but not to larger protein molecules which pass through the capillary walls with great difficulty. Generally speaking, the rate of transfer across the blood-aqueous barrier of different substances depends more on their chemical nature than upon the size of their molecules. In the decreasing order of filtration are: alcohols, sugars, ions, and nitrogenous substances. Some synthetics such as trimethylglucose cross the blood-aqueous barrier at approximately the same rate as metabolites with the same size molecules, illustrating that filtration, and not secretion, is the major factor in some intraocular components. The blood-aqueous barrier in the eye consists of capillaries and secreting ciliary epithelium. The low protein content of the aqueous, .02 percent, is similar to that of the spinal fluid. Following paracentesis, however, the new aqueous contains more protein and less chlorides. The normal aqueous salt content is greater than that of the blood plasma. The intraocular fluid also differs from the blood plasma in its content of the following acids: hyaluronic, ascorbic and lactic. In the posterior segment of the eye the transudate from the choroidal capillaries is insufficient to maintain retinal nutrition. The osmotic pressure of the aqueous is higher than that of the blood plasma. Throughout the vascularized tissues of the eye there is a peculiar and controlled transfer of materials through the cell bodies of the capillaries instead of through their interspaces as in the body generally.

In the exit of the intraocular fluids from the globe the process is not one of diffusion but an undifferentiated flow in bulk allowing free mechanical exit to comparatively large molecules. The pressure in the eye is determined as a hydrodynamic steady-state by the capillary pressure plus an excess of osmotic pressure. The intraocular pressure may therefore be altered by the following changes: secretory activity, capillary permeability, hydrostatic blood pressure and drainage blockade. In both simple and inflammatory primary glaucomas, the author has apparently become more impressed by the importance of the vascular factor.

Chas. A. Bahn.

Feldman, J. B., DeLong, P., and Brown, C. P. **Practical application of surface-active drugs in ophthalmology.** Arch. Ophth. **40**:668-679, Dec., 1948.

A series of surface-active or wetting agents were studied to ascertain their possible usefulness as vehicles for ophthalmic drugs. The agents were first tested on rabbits and then on patients. Tests were made on their bacteriostatic action. It was found that certain wetting agents had no deleterious effect on the eye, but became irritating only when combined with certain ophthalmic drugs. A new preparation, hyamine L4-669, similar to benzalkonium zephiran chloride, was proved to be valuable as an antiseptic by laboratory and bacteriologic

studies and by clinical use in treatment of infections in the human eye. Surface active agents were used as vehicles for a number of ophthalmic drugs. Many proved fairly effective. The relative therapeutic effect of the various combinations is given. The new mydriatic dibutoline sulphate and also tetracaine and sodium penicillin are surface-active.

John C. Long.

Ginsburg, M., and Robson, J. M. **Further investigations on the action of detergents on the eye.** Brit. J. Ophth. **33**: 574-579, Sept., 1949.

Five wetting agents, dodecyl sodium sulphate, ammonium lorol, aerosol O.T., lissapol N, and C 60799, were very effective in increasing the penetration of sulphacetamide into both the living and isolated rabbit cornea and dodecyl seemed to be the most effective. In no case was there actual union of the detergent with the drug but there was destruction of the surface epithelium of the cornea. It is concluded that penetration is enhanced by the detergent's action of solubilising the intercellular cement of the epithelium and it becomes obvious that the clinical use of the detergents is quite limited.

Morris Kaplan.

Kiss, F. **Connection between the blood circulation of the eye and of the brain.** Szemészet **3**:133-143, 1949.

The paper is a continuation of the author's previous communication (Szemészet, 1949, No. 1 and Amer. J. Ophth. 9: 1297, 1949). The ophthalmic vein and the cerebral veins are similarly connected to the intracranial sinus-system. The whole sinus-system with all its veins is under the periodic suction of the thorax via the internal jugular vein. India ink injected into the anterior chamber was absorbed into the ciliary plexus described by the author in living animals as well as in fresh human corpses. In human corpses, intermittent suction on the internal jugular vein was substituted for the natural suction of the thorax. India ink injected into the anterior chamber of the living human eye 25 minutes before enucleation was similarly absorbed by the same ciliary plexus. The canal of Schlemm has only an accessory influence. The author demonstrated that pigment-cells of melanosarcomas in human eyes are absorbed by the same plexus. This is the route of metastases. Gyula Lugossy.

Leopold, I. H., Yeakel, E., and Calkins, L. L. **Corneal vascularization in the gray Norway rat.** Arch. Ophth. **42**:185-187, Aug., 1949.

Vascularization of the midstroma of the cornea occurred in the Norway gray rats, but not in the albino rats, when the two strains were maintained on similar diets and in the same colony. The cause was not definitely determined. Sex had no influence on the incidence of the vascularization. The vascularization increased with age and was most pronounced in Norway gray rats over 500 days old.

John C. Long.

Rosso, S., and Brongnoli, C. **The effects of aneurin (thiamine) on the amplitude of accommodation.** Ann. di ottal. e clin. ocul. **75**:71-82, March, 1949.

By studies made with a specially constructed ergograph Rosso and Brognoli confirmed the positive effect of thiamine on the amplitude of accommodation. The mechanism of the action of the vitamin is uncertain, but its principal action is probably on the ciliary neuromuscular system and not on the lens. One may accept provisionally the hypothesis of De Grosz, according to which the production of acetylcholine is increased and the cellular barrier becomes more permeable to acetylcholine, whence results a greater and more lasting contractility of the ciliary muscle. It is suggested that

thiamine may have therapeutic value in accommodative asthenopia.

Harry K. Messenger.

von Sallmann, Ludwig. **Experimental studies on the vitreous. 1. Experiments on diffusion in the vitreous and on permeability of its surface condensation layer.** Arch. Ophth. **42**:583-595, Nov., 1949.

Part of the author's summary of this excellent experimental work is as follows. 1. The diffusion rate of homologous hemoglobin in undamaged vitreous preparations was increased by temperature increments and by autolytic decomposition of the colloidal system. 2. In general, mixtures of hemoglobin or Niagara blue with hyaluronidase preparations did not diffuse more rapidly in steer vitreous than did hemoglobin or the dye alone. 3. In the pH range from 6 to 8, changes in the pH of the milieu did not noticeably influence the character or rate of diffusion of hemoglobin in the steer vitreous. 4. The surface condensation layer of the vitreous differs in its premeability for hemoglobin from the permeability of the enclosed system and its boundary interphases. 5. Hydrochloric acid penetrated the surface layer and diffused at a higher rate in the vitreous than did sodium hydroxide. The diffusion rate of the weak acid and base exceeded that of the strong acid and base. Ralph W. Danielson.

Del Zoppo, Italo. **The histamine of the aqueous humor of normal human eyes.** Ann. di ottal. e clin. ocul. **75**:55-62, Feb., 1949.

Using the biologic method, Del Zoppo found histamine always present in the aqueous humor of normal human eyes. The quantity varies from a minimum of 0.04 to a maximum of 0.08 gamma per cc., with an average of 0.066. These quantities are very similar to those found in the aqueous of certain animals by Emmelin and Palm and to those quantities established for the blood by other investigators. The comparative study of the amounts of histamine in the aqueous of normal and abnormal eyes should lead to results of biologic and clinical importance. Harry K. Messenger.

4

PHYSIOLOGIC OPTICS, REFRACTION, COLOR VISION

Bornschein, H. **Acuity of night vision in relation to illumination of area surrounding the test field.** Wien. klin. Wchnschr. **61**:675-676, Oct. 21, 1949.

Bornschein studied the problem whether the magnitude of the periodic fluctuations of performance which may be observed in determining acuity of night vision may be reduced by constant weak illumination of the area which surrounds the test field. The acuity of night vision was measured by means of the Nowak-Wetthauer apparatus which consists of a black movable Landolt test ring on a square white background and of a device for weak gradually changeable illumination. A white square area surrounding the test field had been added with a similar device for weak gradually changeable illumination as the one used for the test field. Monocular tests were performed on three persons between the ages of 20 and 30 years. The biostatistic evaluation of the experiments revealed that an illumination of the area surrounding the test field just above the terminal threshold entails a partial lowering of the threshold which may be statistically secured, but it does not entail a real lessening of the fluctuations. This method therefore does not really enrich the practical techniques of examination. Theodore M. Shapira.

Carreras Duran, Buenaventura. **On aniseiconia.** Arch. Soc. oftal. hispano-am. **9**:934-941, Sept., 1949.

Carreras points out that disparity of the retinal or cortical images was a well

known phenomenon for a long time, and that its interest under the new name of aniseiconia is limited to American investigators. Physiologic aniseiconia, due to the unequal distribution and spacing of the retinal elements in the two eyes, and in the temporal and nasal portions of the same eye produces no clinical symptoms, and the symptoms of asthenopia attributed to aniseiconia are not characteristic of this anomaly, and may be caused by refractive errors and heterophoria. In his opinion this condition has only an academic interest, and no clinical significance. Ray K. Daily.

Hardy, L. D. **Investigation of visual space.** Arch. Ophth. **42**:551-561, Nov., 1949.

Since January 1948 the chief problem for investigation by the staff of the Knapp Laboratory for Physiological Optics has been the bases on which space perception and spatial orientation are founded. The work is grounded on Luneburg's "Mathematical Analysis of Binocular Vision," which incorporates new and important concepts regarding the fundamentals of space perception. The author says that the problem is to discover, evaluate and mathematically express the fundamental, basic relationships between visual stimuli and the sensation they arouse, to find and verify the constant factors operating in this relationship and to seek and describe the underlying constant relationships between binocular stimulus and resultant sensation to which all the subsequent psychologic and experiential factors are added. The problem is of much more than academic interest. It is of potentially great importance in the fields of art, architecture, industry and war. If the metric (the rule, the formula, the measuring rod) of visual space can be formulated, one of the oldest and most interesting problems, the sensory perception of three dimensions by binocular vision, will have received considerable clarification.

After technical discussions, the author presents the theory that visual space differs from physical space; that if the latter is Euclidean in our vicinity the former is certainly not; that the metric of visual space closely corresponds to, or is identical with, the metric of Lobatschewsky's hyperbolic geometry; that at least two, and probably more, personal constants enter into this metric; that these constants (refractive errors, aniseikonia, stereopsis, for example) are fairly stable for a given individual but may be modified by such factors as age, correction of refraction, experience and other factors. Ralph W. Danielson.

Jonkers, G. H. **Some data concerning Verhoeff's quantitative test for measuring the acuity of binocular stereopsis.** Ophthalmologica **118**:182-193, Sept., 1949.

One hundred individuals, visually well qualified to serve as normal controls, have been tested with Verhoeff's instrument (Arch. of Ophth. 28:1000, 1942). By means of purely binocular clues the examinee has to recognize relative depth differences exhibited by vertical stripe patterns. The greatest distance at which these depth differences were recognized in all patterns is a measure of the examinee's acuity of binocular stereopsis. To facilitate the statistical treatment Jonkers has calculated a nomogram which permits conversion of the test distance into binocular parallactic angle (taking the examinee's pupillary distance into consideration). The variations of this angle within the population of 100 controls followed the normal (Gaussian) binomial distribution curve. The most frequent parallactic angle was 16.4 seconds of arc (for a PD of 64 mm.).

Peter C. Kronfeld.

Junes, Emile. **The phenomenon of Maxwell.** Ann. d'ocul. **182**:740-756, Oct., 1949.

The phenomenon of Maxwell is among the interesting entopic phenomena which involve foveal function. It consists essentially of a visible circle surrounded by a darker halo after fixing a faint light with dark background. This may be accomplished by viewing the moon at night or a small artificial light with a blue background. The phenomenon or spot of Maxwell is apparently due to the diffusion of visual purple between the rods and cones at the outer margin of the fovea. In the first phase which is brief, a dark spot without color is observed. In the second stage a red-brown circle with a bluish halo which becomes white is seen. In the third and longest phase, the halo becomes yellowish. Several theories of color vision are discussed, including those of Parinaud, Young, Woll and Von Studnitz. The author believes that foveal and extrafoveal vision depend upon essentially separate mechanisms and that the phenomenon or spot of Maxwell occurs at their junction.

Chas. A. Bahn.

Maione, Mario. **Contact lenses and aphakia. Optical notes and practical considerations.** Ann. di ottal. e clin. ocul. **75**:127-137, April, 1949.

In aphakia a contact lens may permit perfect vision at both distance and near without the aid of a supplementary lens. Maione has observed this phenomenon in three patients and believes it due to a slight decentration of the lens in convergence, which brings an optically more powerful zone of the lens into play. In unilateral aphakia a contact lens is the only practical means of restoring binocular vision. Excessive aniseikonia must be avoided, and a practical method of computation of curvatures is given.

Harry K. Messenger.

Rössler, F. **The cobalt glass test of Helmholtz.** Ophthalmologica **118**:149-160, Sept., 1949.

The optical phenomena produced in the schematic human eye by placing a piece of cobalt glass in the path of incident white light were first worked out theoretically and described by Helmholtz in his "Physiological Optics." He thought that the relative size of the blue and red blur circles which form on the retina under those conditions, could serve as a basis for a subjective refraction test. Actually, the visual sensations elicited in nonaccommodating eyes by small light sources viewed at short distances corresponded closely to Helmholtz's theoretical expectations. Under conditions of distance vision, however, the subjective observation through the cobalt glass, proved very complex and difficult to interpret. As a method of determining the refractive state the cobalt test fell into oblivion. Rössler, one of the main proponents of the cobalt glass as a refraction test, reviews some of the changes in our understanding of the imagery in human eyes which have occurred since the days of Helmholtz. Some of these changes have greatly contributed to an understanding of the phenomena observed with cobalt glass filters.

Peter C. Kronfeld.

Treissman, H. **Some observations on the causation and elimination of Sattler's veil.** Brit. J. Ophth. **33**:555-567, Sept., 1949.

The cause of the veiling is the presence of a lip at the corneoscleral junction which causes a ring of pressure that results in sealing off the fluid which is in contact with the cornea. This stagnant fluid becomes cloudy and irritating. In some patients the conjunctiva is more prone to edema and too tight a conjunctival fit causes edema which results

in the sealing off of the corneal portion. A third cause of the misting is too great a corneal clearance which results in a slowing of the exchange with tears thus exposing the fluid to absorption of CO_2.

Morris Kaplan.

5

DIAGNOSIS AND THERAPY

Alagna, G., and Recupero, E. **The treatment of some ocular diseases by means of the transfusion of hematologically incompatible human blood.** Ann. di ottal. e clin. ocul. **75**:181-209, June, 1949.

Thirty cases are presented of various ocular diseases treated with transfusions of small amounts of hematologically incompatible human blood. The amounts varied from 3 to 15 cc. at one transfusion, and the total amount ranged from 15 to 45 cc. Favorable responses were noted in cases of phlyctenular keratoconjunctivitis, superficial and deep keratitis with and without suppuration or hypopyon, iritis, post-traumatic iridocyclitis, uveitis, sympathetic ophthalmitis, and hemorrhages into the vitreous. Best results were obtained in diseases of recent onset, especially if on an allergic basis, and in young persons. In almost all cases a mild focal reaction of brief duration occurred. The mechanism of action of this new therapeutic method is thought to be that of nonspecific protein therapy in general. The transfused blood presumably stimulates the normal defenses of the body and exerts also a marked nonspecific desensitizing antiallergic action. It is thought that a series of mild colloidoclastic crises induced by the incompatible blood causes the cells of the body to lose their exaggerated excitability.

Harry K. Messenger.

Alvarez Alvarez, Abundio. **Local penicillin therapy in ophthalmology.** Arch. Soc. oftal. hispano-am. **9**:974-1006, Sept., 1949.

This is principally an exhaustive review of the literature. To illustrate the effectiveness of massive doses of penicillin given subconjunctivally, Alvarez reports in detail a severe bilateral luetic iridocyclitis, which responded spectacularly to this method of penicillin administration. In three cases of traumatic infected corneal ulcer it was equally effective.

Ray K. Daily.

Atkinson, W. S. **Use of hyaluronidase with local anesthesia in ophthalmology.** Arch. Ophth. **42**:628-633, Nov., 1949.

Hyaluronidase depolymerizes and hydrolyzes hyaluronic acid, a mucopolysaccharride acid, which was first isolated by Meyer and Palmer from bovine vitreous humor. In animal tissue hyaluronic acid seems to bind water in interstitial spaces and hold cells together in a jelly-like matrix which obstructs diffusion. The addition of hyaluronidase causes a rapid dispersion of fluid when injected into tissues. The rapid dispersion is brought about by a depolymerization and hydrolysis of the hyaluronic acid gel. The reduction in viscosity removes one of the barriers to diffusion of fluid and allows it to permeate the tissues more rapidly and widely. In 109 eyes preoperative injections of an anesthetic solution containing hyaluronidase were given. The surgical procedures included minor operations on the lids, cataract extractions, enucleations with implants and operations for glaucoma, retinal detachment and strabismus.

With the addition of hyaluronidase to injections of an anesthetic solution of procaine and epinephrine, there was a greater diffusion of the anesthetic, anesthesia occurred more rapidly and lasted as long, there was less ballooning of the

tissues, and the area of anesthesia was greater. More effective akinesia of the orbicularis and extraocular muscles was obtained. Hypotony was pronounced after cone injections and was occasionally sufficient to make the cataract extraction more difficult but safer, and vitreous was less likely to present. Ischemia due to epinephrine was quickly followed by erythema of brief duration. The eye frequently became red after a cone injection.

Ralph W. Danielson.

Barraquer Moner, J. I. **First impressions on some aspects of the new tissue therapy of Filatov.** Arch. Soc. oftal. hispano-am. **9**:861-869, Aug., 1949.

The basis and technique of tissue therapy are briefly reviewed, and the results of the author's personal experience reported. This comprises 108 cases with a period of observation extending over 3 months, 88 over 5 months, 62 over 5 months, and 9 over 6 months. Patients with less than a three months period of observation are not included in this report. In retinitis pigmentosa 25 percent showed appreciable and 25 percent definite improvement; 30 percent of the patients reported a subjective benefit, especially in color contrast and twilight vision, without any objective evidence of improvement. In 20 percent there was no effect. Patients with chorioretinitis of various origin benefited to the same extent as those with retinitis pigmentosa. In five cases of optic atrophy there was no effect. In uveitis, this therapy hastened absorption of exudates and healing. In acute disseminated choroiditis the absorption of exudate and subsidence of inflammation was spectacular. Barraquer has the impression that this therapy acts favorably by lysis of connective and newly formed tissue. Eleven illustrative cases are reported. (1 visual field.)

Ray K. Daily.

Belmonte Gonozales, José. **Autofundoscopy.** Arch. Soc. oftal. hispono-am. **9**: 699-702, July, 1949.

The history of autofundoscopy is briefly reviewed, and apparatus for its performance is described which consists essentially of two plane mirrors mounted on a stand so that their separation and the angle between them can be varied. The mirrors are so arranged that the right eye sees the image of the left eye and vice versa; an ophthalmoscope is then used just as if the eye were that of a patient. One can examine one's own eye with the direct or the inverted image. (5 figures.)

Ray K. Daily.

Buerger, Leopold. **The dangers of spoiled ointments and oils containing infectious and toxic material and their recognition through Ranzol.** Klin. Monatsbl. f. Augenh. **115**:55-56, 1949.

The author cites cases of hoof and mouth disease in human beings, as well as of erysipelas and botulism, which were transmitted through medicinal ointments. To recognize spoilage he recommends the use of the preparation "Ranzol" which produces green fatty acid crystals in spoiled pharmaceuticals.

Max Hirschfelder.

Cogan, D. G. **A simple method for temporary closure of the lids.** Arch. Ophth. **42**:188, Aug., 1949.

In cases in which it is desirable to close the lids for a few days to a few weeks, "glueing" has been found to be a satisfactory procedure. The "glue" used is the standard Duco cement. The procedure consists in closing the patient's eyes and applying by means of a tooth applicator several layers of the cement to the lashes of the upper lids, sealing them down to the cutaneous surface of the lower lid. Time is allowed for drying of each layer.

The cast provides a firm cohesion of the lids lasting 3 to 5 weeks. John C. Long.

Collado, Palomar. **Local bleeding in ophthalmology.** Arch. Soc. oftal. hispano-am. **9**:885-892, Aug., 1949.

The application of leaches in ophthalmology is reviewed without adding anything new. Ray K. Daily.

Gomez da Silva, Avelino. **A new form of biomicroscopic examination "retro-transillumination"** (in Portuguese and in English). Arq. brasil. de oftal. **12**:87-97, 1949.

The author uses a new adaptation to Comberg's slitlamp of Koeppe's mirror as employed in Poser's slitlamp, aiming at a simplified and more efficient method for examination of the retina. (3 figures, 1 in color.) W. H. Crisp.

Gürtler, E. **Cotton threads in anterior chamber following surgical intervention on the eyeball.** Wien. klin. Wchnschr. **61**: 686-689, Oct. 21, 1949.

Gürtler reports 26 cases in which cotton threads were observed in the anterior chamber after operation for cataract and on one after Elliot's trephining for glaucoma during a period of 3½ years. Cotton threads were observed in 26 of 1,500 patients who were operated on for cataract. Follow-up examinations showed that the cotton threads in the anterior chamber are tolerated by the eye without irritation. Mild hyperemia of the vessels of the iris in the neighborhood of the cotton threads was observed occasionally for a short period, but the postoperative iritis which developed in two of the author's cases was caused by the operation itself and did not result from irritation by the threads; the iritis subsided while the threads remained in the chamber. The contents of the anterior chamber do not change the physical properties of the cotton threads and the movements of the iris do not have any noteworthy effect on their shape. Theodore M. Shapira.

Halberg, G. P. **Simple camera support for the operating theatre.** Brit. J. Ophth. **33**:780-781, Dec., 1949.

A simple support for the camera for use in the operating room is presented. This consists of a single diagonal and vertical iron rod, and the latter is clamped to the operating table. (2 figures.)

Orwyn H. Ellis.

Marin Amat, M. **Cocaine crystals in ocular theapeutics.** Arch Soc. oftal. hispano-am. **9**:931-933, Sept., 1949.

Marin calls attention to the usefulness of cocaine crystals for anesthesia of sensitive ocular areas, as in removal of post-operative sutures, acute glaucoma and exploration of the lacrimal passages. The profound cocaine anesthesia eliminates the axon reflexes which are associated with the production of histamin and extreme vasodilating reactions.

Ray K. Daily.

Marin Enciso, M., and Munoz Pato, F. **Methyl antigen in ophthalmology.** Arch. Soc. oftal. hispano-am. **9**:715-719, July, 1949.

From an experience of 150 cases of ocular tuberculosis the authors conclude that this tuberculin filtrate is a beneficial agent in the treatment of ocular tuberculosis and that properly used it produces no general or focal reactions. In this respect it is superior to old tuberculin.

Ray K. Daily.

Mazzotti, Luis. **The treatment of oncocercosis.** An. Soc. mex. de oftal. **23**:19-25, Jan.-March, 1949.

The author has tried Hetrazán (1 diethylcarbamyl 4 methyl piperazine) in the treatment of filariasis. He finds the drug nontoxic in the doses recommended,

although in about half the cases treated the adult organisms were modified in their vitality. Of 65 individuals treated only 7 were under observation a sufficient length of time. The dose recommended is by mouth 4 mg. per kilo of body weight three times daily, beginning with one-third of the dose on the first day. Since the action of the drug on the adult organisms is not clearly demonstrated, it is still advisable to extirpate the subcutaneous nodules before administration of the drug. (References.) W. H. Crisp.

Oxilia, Efisio. **Tyrothricin and its use in ocular infection.** Giorn. ital. oftal. **2**: 214-224, May-June, 1949.

In 9 cases of ulcerous ciliary blepharitis and blepharoconjunctivitis recovery followed the use of tyrothricin in 3, improvement in 2 and failures in 4. In 10 cases of conjunctivitis there were 7 recoveries and 2 failures and the degree of success was similar in chronic dacryocistitis, keratoconjunctivitis with impetigo of the face, and in infectious corneal lesions.

The antibiotic effect of tyrothricin is limited to gram-positive bacteria and, because of the poor absorption of the drug, the applications have to be made topically on the infected area. On the other hand it is thermostable, active even in the presence of drugs containing heavy metals or alcohol, non-toxic in local application, and active against germs which have become penicillin or sulphanilamide resistant. Vito La Rocca.

Penido Burnier Jr. **Tonometry. Contribution to its execution.** Arq. do Instituto Penido Burnier **8**:113-119, June 1, 1949.

The author reviews the conclusions of the Committee on Standardization of Tonometry of the American Academy of Ophthalmology and Otolaryngology, urges adoption of the standards set up by that organization, and calls upon ophthalmologists to have their tonometers standardized. W. H. Crisp.

deRoetth, Andrew. **Penetration of aureomycin into the eye.** Arch. Ophth. **42**: 365-372, Oct., 1949.

Experiments were carried out to ascertain the penetrability of aureomycin into the normal rabbit eye, with the following results. 1. After corneal bath no aureomycin was detected in the aqueous. 2. Iontophoresis and subconjunctival injection produced low levels in the aqueous. Iontophoresis was fairly well tolerated by the eye, but subconjunctival injection was irritating to such an extent that it was considered contraindicated. 3. Aureomycin did not penetrate into the eye when given orally or intramuscularly. 4. The cornea, sclera, iris and ciliary body, aqueous, vitreous and spinal fluid showed appreciable concentrations of aureomycin when large amounts were given intravenously.

As compared with other antibiotics, aureomycin is more irritating and penetrates less readily into the eye; but once it has crossed the blood-aqueous barrier, it remains longer in the ocular fluids and tissues. John C. Long

Riverall Noble, Bertha. **The ocular attack in oncocercosis. Ocular manifestations during treatment with Hetrazán.** An. Soc. mex. de oftal. **23**:26-31, Jan.-March, 1949.

The ocular reactions presented during treatment with Hetrazán were almost exclusively of the anterior segment and allergic in type. Are they produced by the drug? Probably only through the action of the drug in killing many organisms, because similar manifestations are seen extensively in individuals not treated with the drug. A long period of study appears necessary as to the problem of toxicity of Hetrazán. W. H. Crisp.

Simonelli, Mario. **Research on the permeability of the hemato-ophthalmic barrier.** Giorn. ital. oftal. 2:185-192, May-June, 1949.

Continuing his research on the effects of various vitamins on the permeability of the hemato-ophthalmic barrier, the author reports the results of the administration of vitamin P_2 in doses of 200 mgr. daily in many normal subjects and some with an increasing pathologic ciliary permeability. In these latter the reduction of permeability was particularly evident, especially in some cases of diabetic retinitis; even in 7 of 12 normal subjects the injection of Idro P_2 caused an appreciable lessening of the permeability. The vitamin treatment was carried out for 15 days days; the reaction on the ciliary permeability was noted on the fifth day. The effect of the P_2-like substances and of vitaman P_2 differed from that of Citrin and Rutin. Vito La Rocca.

Uribe Troncoso, Manuel. **Comparative physiology of elimination of the aqueous humor in mammalia and the role of the canal of Schlemm.** An. Soc. mex. de oftal. 23:63-79, April-June, 1949.

The author traces the changed conception of the nature of aqueous secretion from his work in 1909 through the work of various authors down to the present day. In lower mammalia aqueous elimination occurs through the intrascleral meshwork along the ciliioscleral sinus, whereas in man it occurs through Schlemm's canal and the intraocular plexuses. (6 figures, references.)

W. H. Crisp.

6

OCULAR MOTILITY

Mellick, A. **Convergence. An investigation into the normal standards of age groups.** Brit. J. Ophth. 33:755-763, Dec., 1949.

Investigations of convergence were made with the synoptophore and a variable-prism stereoscope. In the measurement of the horizontal ductions there is no essential difference in the results obtained using both simple fusion and stereoscopic targets. Results in different age levels varied only slightly. In abduction similar results were obtainable at near on both instruments, while at distance the results on the synoptophore were about one-third higher in value than on the variable-prism stereoscope. In adduction the results on the synoptophore were about double those obtained on the other instrument. Orwyn H. Ellis

7

CONJUNCTIVA, CORNEA, SCLERA

Allen, J. H., and Barrere, L. E. **Prophylaxis of gonorrheal ophthalmia of the newborn.** J.A.M.A. 141:522-526, Oct. 22, 1949.

Bacterial studies of the antepartum cervix, and of the newborn infant's conjunctiva at birth, and 24 hours after the local use of silver nitrate or penicillin have shown that silver nitrate produces no more harmful effects than penicillin. Until more work is done in areas where the incidence of gonorrhea is higher, 1-percent silver nitrate should continue to be used at birth, and again after the infant is bathed. Francis M. Crage.

Almeida, A. **Keratoconus and persistent thymus.** Arq. de Instituto Penido Burnier 8:85-93, June 1, 1949.

In 102 patients, from 8 to 39 years old, the author was able to demonstrate, after anterior pneumomediastinum, a hypertrophy of the thymus. He contrasts these cases with X-ray plates from ophthalmologically normal patients in whom there was no radioscopically demonstrable thymus. It was his impression that radiotherapy reduced the thymus and improved the corneal symptoms, but he admits that the period of five years during

which he has studied these cases is of doubtful adequacy for a final conclusion. Reviewing Vasquez Barriere's study of the subject, he was unable to find a single case of positive Frei test, even with 0.3 cc. of antigen. W. H. Crisp.

Bonavolontà, A. **Dermatitis of Duhring-Brocq with ocular manifestations.** Giorn. ital. oftal. 2:169-184, May-June, 1949.

After an extensive survey of the literature on this debated form of benign pemphigus the author describes a case occurring in a boy of 13 years, in which the skin lesions appeared in early life and the eye lesions at the age of 11 years. The patient was treated for about two years with sulfanilamides, electrolysis for the trichiasis, penicillin, vitamin A, vaccines, autohemotherapy, and Roentgen irradiation of the limbal region and cervical ganglia. The right eye in spite of all treatment ended with a total symblepharon and xerosis, while the right eye showed some improvement and no opacification of the cornea. Vito La Rocca.

Brown, A. L., Nantz, F. A., Town, A. E., and Tassman, I. S. **Symposium: The use of fibrin coagulum fixation in ocular surgery.** Tr. Am. Acad. Ophth., Nov.-Dec., 1949.

I. Brown, A. L., and Nantz, F. A. In retinal detachment. pp. 126-130.

The temporary adhesion of tissues is facilitated by fibrin. Its use is of great value in recent retinal detachments, in cataract extractions and in external wounds. The procedure which the authors evolved in the treatment of retinal detachment consists of retrobulbar anesthesia, the formation of a conjunctival flap, approximately 20 superficial and 4 perforating diathermic punctures in the region of the detachment, the removal of subretinal fluid, and the injection of 2 min. of the patient's plasma containing .12 mg. fibrinogin in the four perforating punctures. In a series of 30 unselected cases of retinal detachment, 60 percent were considered cured in that the vision was 20/100 or more with complete retinal attachment for six months or more; 10 percent were improved and 30 percent were failures.

II. Town, A. E. In intraocular surgery. pp. 131-133.

In cataract extraction the use of fibrin tends to prevent delayed wound closure with resultant leaking, iris prolapse, hemorrhage and epithelial implantation in the anterior chamber. It may also be employed as a substitute for corneal sutures, thereby reducing trauma. Results obtained in some cases of keratoplasty, glaucoma, traumatic and plastic surgery justify the use of fibrin coagulum. In the author's service at the Jefferson Hospital, fibrin closure is routinely used where possible. To collect the plasma 45 cc. of blood is withdrawn with a syringe containing 5 cc. of a sterile solution of 3.8 percent sodium citrate. The fluid is centrifuged and 3 cc. of plasma is stored in each of several 5-cc. ampules to which 1.5 cc. of sterile water is added. After lens extraction, 1 or 2 drops of plasma solution are applied near the limbus above, nasally and temporally and 1 or 2 drops of thrombin solution are added.

III. Tassman, I. S. In keratoplasty. pp. 134-139.

The author has used fibrin coagulum fixation in 112 cases of which 15 were lacerations and wounds and 8 were keratoplasties. In the latter fibrin coagulum was as effective as the usual sutures.

Chas. A. Bahn.

Casanovas, José. **A contribution to the study of blood-staining of the cornea.** Arch. Soc. oftal. hispano-am. 9:942-966, Sept., 1949.

The pathogenesis, etiology, histopathology and treatment are reviewed, and

nine cases reported. The conclusions from a review of the literature and the author's experience with these nine cases are that blood staining of the cornea presents a definite clinical and pathologic picture, which threatens patients with extensive hemorrhage into the anterior chamber, and is especially apt to occur in the presence of hypertension. Having been absorbed, it may recur following a very insignificant trauma, and reabsorption may them proceed more rapidly because of the presence of newly formed blood vessels. The blood may be absorbed very rapidly in vascularized corneal cicatrices, losing in these areas its usual circular form. In old cases calcareous degeneration may develop in the blood stained areas. In the treatment of this condition paracentesis may lead to sudden extensive hemorrhage and should be avoided. The treatment suggested is coagulant therapy followed by absorbtion-promoting agents; of the latter, subconjunctival injections of mercury cyanide, and iontophoresis with potassium iodide appear most useful.

Ray K. Daily.

Cortes, Hernán. **The application of oidiumicin in ulcers with hypopyon.** Arch. Soc. oftal. hispano-am. **9**:893-894, Aug., 1949.

A man, twenty years old, developed a serpiginous ulcer in his only eye. In spite of heroic treatment with all known medicaments, the hypopyon increased and the ulcer progressed until it perforated on the 16th day after its onset. The perforation was covered with a conjunctival flap; four days later the flap retracted, and the hypopyon was found to have increased. In desperation it was decided to try a subconjunctival injection of ½ cc. of oidiumicin. On the following day the hypopyon was scarcely visible, and the conjunctivo-ciliary congestion was markedly diminished; the injection was repeated every 48 hours and the fourth injection was given after an interval of 72 hours. At the end of ten days the ulcer was covered with epithelium, and the patient was discharged with a leucoma.

Ray K. Daily.

Eyb, C. **Trepanation according to Elliot for serpiginous ulcer.** Wein. klin. Wchnschr. **61**:678-679, Oct. 21, 1949.

Trephining by Elliot's method was performed on 12 patients with serpiginous ulcer on the third day, and on 13 patients on the eighth day. Trephining was delayed in those cases in which improvement seemed to result from common treatment. Healing occurred in two patients of the first group and nine of the second. Improvement followed by recurrence, was observed in four patients in each of the groups and was probably due to occlusion of the opening. Final recovery resulted after treatment with penicillin, puncture of the anterior chamber or spontaneous perforation. There were six failures in the first group and none in the second group. Theodore M. Shapira.

Fleischner, F. G., and Shalek, S. R. **Conjunctival and corneal calcification in hypercalcemia. Roentgenologic findings.** New England J. Med. **241**:863-865, Dec. 1, 1949.

Lesions are seen in the cornea and in the conjunctiva in hypercalcemia. The conjunctival lesions are small glass-like particles in the region of the palpebral fissure. In the cornea there are hazy, grayish, granular epithelial and subepithelial opacities concentric with the limbus on either the nasal or the temporal side. These deposits are calcium phosphate. In the case reported the lesions were typical but the etiology of the hypercalcemia was undetermined. By the use of the bone-free X-ray technique which is described in detail, calcification was demonstrated in the sclera as plump rod-like deposits 2 to 3 mm. in length. In the

corneal limbus this calcium appeared as a solid homogeneous dense shadow of less than 1 mm. in width and 7 mm. in length. (3 figures.) H. C. Weinberg.

Garcia Miranda, Ramon. **Virus Newcastle and the eye.** Arch. Soc. oftal. hispano-am. **9**:720-725, July, 1949.

The literature on Newcastle disease in chickens and the reports of human conjunctivitis caused by the same virus, and traced to the handling of infected chickens, are reviewed. The symptoms in man are unilateral slight palpebral edema, subcutaneous ecchymosis, marked congestion of the tarsal and fornix conjunctiva, with slight papillary hypertrophy, swelling of the caruncle and the semilunar fold, chemosis of the bulbar conjunctiva and subconjunctival hemorrhages. The subjective discomfort and secretion are comparatively mild. There is no ciliary injection and no involvement of the cornea or iris. Preauricular adenopathy is constant, and smears are negative. The onset of the infection may be accompanied by general malaise or low fever, and the disease runs its course in eight or ten days. There appears to be no contagion from man to man. Personal experiments with this virus are reported. During an epidemic in chickens the possibility of human contagion should be kept in mind. (1 figure.) Ray K. Daily.

Mejer, F. **Allergic eczema of eyelids due to streptomycin as occupational disease.** Wien. klin. Wchnschr. **61**:702-703, Oct. 21, 1949.

Mejer reports the occurrence of dermatitis of the eye-lids associated with considerable itching and more or less severe conjunctivitis and lacrimation in three nurses, who prepared streptomycin solutions. Noteworthy was the increased cutaneous scaling. The patients also had photophobia and severe headache. The cutaneous tests with streptomycin (100 units intracutaneously) on two of the nurses and normal controls demonstrated the allergic nature of the reaction. Antistin-Privin drops proved very effective in the treatment of the allergic conjunctivitis. The toxicity of the single preparations of the industrially manufactured streptomycin varies in spite of chemical and optical identity of the crystallized streptomycin. The cause is the heating of the drug in the course of the procedure which results in the development of toxic isomers. The latent period of the local allergic reaction varies from about six to thirty weeks. Theodore M. Shapira.

Mendoza Gonzales, E., and Avales, G. E. **Pathogenesis of inflammatory disorders of the sclera.** An. Soc. mex. de oftal. **23**:38-47, Jan.-March, 1949.

The usual antirheumatic treatments of septic foci frequently fail, or produce in some cases unstable results. Desensitization of the organism with extremely small doses of tuberculin produce more favorable results. Treatment should be continued for a more or less considerable period of time. W. H. Crisp.

Oxilia, E. **Psoriatic keratitis.** Giorn. ital. oftal. **2**:122-128, March-April, 1949.

The author describes the clinical and anatomic findings of the cornea in psoriasis. There are marginal vascularized foci, and smaller avascularized central foci associated with a thickening of the epithelium, with many points of superficial erosion, erosion of the subepithelial superficial stroma and deeper opacities. The author thinks that the dermatosis affects the superficial parenchyma and that the deep lesions are secondary manifestations. Vito La Rocca.

Pascheff, M. **The progressive annual and concentric form of pannus vernalis.** Arch. d'opht. **9**:596-598, 1949.

Pascheff describes a pannus occurring

in a girl of 13 years suffering from vernal catarrh since the age of 6. Each cornea showed an annular fibropapillary pannus with little or no limbal hypertrophy. The visual acuity was reduced to 2/50. At operation the most hyperplastic portions of the pannus of the right eye were removed and on section showed a marked fibropapillary hyperplasia. The author concludes that there is a true pannus of vernal catarrh which in its most malignant form is annular and may arise without hyperplasia of the limbus.

Phillips Thygeson.

Pascheff, M. **The dendritic melanocyte of the limbus.** Arch. d'opht. 9: 599, 1949.

The author states that in vernal catarrh there is often a pigmented circular zone around the cornea of each eye. This limbal zone is often injected and more or less hyperplastic. In histologic sections two types of melanocyte are seen in the epithelium. One type consists of the basal pigmented cells, the melanoblasts of the conjunctiva, while the other, discovered by Pascheff in 1907, is a cell with dendritic processes and a round or oval nucleus which lies between the cells of the basal layer of the epithelium. They are found in the pathologic conjunctiva, particularly in vernal catarrh during the period of greatest activity.

Phillips Thygeson.

Pillat, A. **Cicatrization of conjunctiva (conjunctivitis atrophicans diffusa) in poikiloderma: contribution to aspects of poikiloderma of mucous membranes.** Wien. klin. Wchnschr. **61**:703-706, Oct. 21, 1949.

Pillat cites reports on the association of poikiloderma with cataract, on the involvement of the eyelid in the cutaneous process, and on the appearance of atrophic spots on the retina and of peripapillary edema in poikiloderma. The available literature indicates that involvement of the eye in poikiloderma occurs only in Jacobi's type, that is, in poikiloderma vascularis atrophicans, but not in Civatte's type which is localized in face and neck, nor in the poikilodermatomyositis of Petges.

Pillat describes a case in a new localization, namely in the conjunctiva. The patient was a man, aged 35, who presented the typical picture of poikiloderma vascularis atrophicans of Jacobi's type. The cutaneous lesion extended to the skin of both eyelids. The growth of eyebrows and lashes was scanty and a cicatricial shrinkage of the conjunctiva of the lids existed, which simulated a cicatricial trachoma with pannus and trichiasis. Changes in the lens were absent. The cicatricial changes on the conjunctiva dominated the clinical picture to such an extent that one could designate it as a conjunctival poikiloderma and other causes of cicatrization were ruled out.

Although the bulbar conjunctiva may have a normal appearance, slit lamp examination reveals beginning cicatrization of the conjunctiva, the sclera and the conjunctival leaf of the cornea. The bulbar conjunctiva shows increased density and glistening; in the region of the palpebral fissure it is turbid and slightly pigmented. The blood current in the conjunctival vessels suggests that either the vessels no longer have a contractile layer or cicatrization prevents contraction. The superficial layers of the cornea reflect the light of the slitlamp much more than is normal. An atrophic process involves the entire conjunctival sac. The author suggests for the poikiloderma of the conjunctiva the term conjunctivitis atrophicans diffusa. The poikiloderma is not limited to the conjunctiva. The mucous membranes of lips, mouth, tongue and nose are also involved.

Observations on this patient indicate that involvement of the skin and of the mucous membranes need not be of the

same degree of severity and also corroborates that eyebrows and lashes are either missing or deficiently developed in poikiloderma. It is noteworthy that in the presence of severe poikilodermal shrinkage of the conjunctiva the lens was completely intact. The concurrence of hemophilia with poikiloderma, as in the reported case, is regarded as further proof that poikiloderma is generally a dyshormonal systemic disease. The general involvement of ectodermal tissues is proved by the fact that the development of the teeth may be inadequate or that there may be rapid decay of the teeth.

Theodore M. Shapira.

Purtscher, Ernest. **"Intermittent corneal edema" as manifestation of keratoconjunctivitis sicca.** Wien. klin. Wchnschrift. **61**:709-710, Oct. 21, 1949.

Purtscher presents the case of a man, aged 31, who has been under his observation for about three years on account of intermittent edema of the cornea of both eyes. The epithelium is never entirely normal. It is uneven, shows delicate gray stippling and some of it stains with fluorescein. Visual acuity improves rapidly when tears wash and smooth out the epithelium.

Primary keratoconjunctivitis sicca occurs mostly in women of menopausal age. The author raises the question whether the case of his patient is unusual. A critical survey of the literature gave him the impression that similar observations have been described under various diagnoses.

Theodore M. Shapira.

Silva, Linneu. **Large corneal leproma.** Arq. do Instituto Penido Burnier **8**:120-124, June 1, 1949.

The author describes a typical case of advanced corneal leproma in an Italian immigrant aged 65 years. (4 figures.)

W. H. Crisp.

Thomas, C. I. **Corneal transplantation in cases of aphakia and ectopia of the lens.** Arch. Ophth. **42**:389-401, Oct., 1949.

Apakia and ectopia of the lens present special problems when corneal transplantation is performed. The author's experience in such cases is summarized as follows. 1. In cases of combined corneal leukoma and cataract the corneal transplantation should be done before the cataract is removed. 2. Corneal transplantation can be performed on apakic eyes that are properly selected and prepared, and when proper instrumentation is used for the operation. 3. Ectopia of the lens also presents the problem of loss of vitreous, which must be prevented for the best results. Instruments are shown and the technique is outlined for corneal transplantation in either the aphakic eye or the eye with ectopia of the lens. A special spatula is inserted into the anterior chamber. The spatula may be steadied by the use of a magnet. (9 figures.)

John C. Long.

8

UVEA, SYMPATHETIC DISEASE, AQUEOUS

Gonzalez Pola, A. M. **Notes on the etiologic diagnosis of iridocyclitis.** Arch. Soc. oftal. hispano-am. **9**:967-973, Sept., 1949.

Gonzalez comments on the difficulty of determining the etiology of iridocyclitis, and advocates the application of the new diagnostic procedures, such as the study of the capillary ocular permeability, Amsler's cytologic studies of the aqueous humor, and Mester's test for rheumatism. The author found that the ocular capillary permeability, tested by an intravenous injection of flourescein, was increased in nontuberculous iridocyclitis; in tuberculous iridocyclitis, with a tendency to hypertension, and a disturbance in the venous circulation, the capillary permea-

bility is diminished. The uveal reaction to injections of tuberculin and typhoid vaccine is also of diagnostic value; in tuberculous iridocyclitis an intradermal injection of tuberculin leads to a definite reduction in intraocular tension, while typhoid injections aggravate the process. On the other hand eyes react well to typhoid injections in iridocyclitis caused by focal infection. The salient points of the cytologic studies of Amsler and Verrey on the aqueous humor in the various types of iridocyclitis are reviewed.

Ray K. Daily.

Morgan, O. G. **Some cases of inflammation in the other eye after cataract extraction.** Tr. Ophth. Soc. U. Kingdom **67**:369, 1947.

The author reports five patients in whom extracapsular lens extraction was followed by iridocyclitis in the other eye after a latent period of a few weeks or months. The clinical course in each was extremely like that of a sympathetic inflammation, though perhaps there was a greater tendency to increased tension. All the affected eyes were removed except one and it was blind. These cases seem to form a definite group allied to sympathetic ophthalmia.

Beulah Cushman.

9

GLAUCOMA AND OCULAR TENSION

Arato Istvan. **Angiodiathermy and its application in glaucoma.** Arch. Soc. oftal. hispano-am. **9**:746-758, July, 1949.

Under the name of angiodiathermy the author describes a new procedure which has for its objective a restriction of the production of aqueous humor through the obliteration of the anterior and the large posterior ciliary arteries. The vessels are coagulated by diathermy punctures at the level of the insertion of the internal and external recti. A diathermy needle, 1.5 mm. in diameter, is introduced obliquely backwards, immediately in front of the insertions of the muscle tendons, which are exposed in the usual manner; 10 to 12 punctures are made. Then punctures perpendicular to the sclera are made in small circles at points equidistant from the limbus and the muscle insertions to reach the posterior ciliary arteries. The author found this procedure ineffective in congestive glaucoma, acute or chronic, but excellent in noncongestive glaucoma. The effect of the operation increases with the cicatrization of the vessels. In three cases of acute glaucoma the immediate fall in tension was maintained for only a few days. In five cases of chronic congestive glaucoma, one of buphthalmos and two of secondary glaucoma, the immediate drop in intraocular tension was also only transitory. On the other hand, in four cases of chronic noncongestive glaucoma, the results were excellent and stable; cyclodialysis performed on one eye and angiodiathermy on the other permitted a comparative assessment of the value of the operation, and demonstrated that it is as effective as cyclodialysis and less traumatizing. The reduction in the intraocular tension for at least two years indicates that the operation acts not by producing a paralysis of the uveal vessels, but by a permanent obliteration, which is not replaced by a collateral circulation. The difference in the behavior of the intraocular tension in acute and chronic glaucoma following this operation indicates that there is a basic difference in the etiology of the two diseases. (8 tension curves.) Ray K. Daily.

Del Barrio, A. **Observations on sympathetic ophthalmia.** Arch. Soc. oftal. hispano-am. **9**:839-849, Aug., 1949.

Three cases of sympathetic ophthalmia following cataract extraction are re-

ported. In one case the operated eye was enucleated five months after the operation, when the sympathizing eye had a fully developed iridocyclitis; this eye was lost. In the second the operated eye was enucleated two months after the operation because of a painful iridocyclitis. Five days later the first inflammatory symptoms appeared in the second eye; during the course of the disease an iridectomy and sclerectomy were performed for the relief of raised ocular tension; when the inflammatory symptoms subsided a pre-existing cataract was extracted, with a final visual acuity of 5/30. The third patient presented himself with a sympathetic ophthalmia of the left eye, following a cataract extraction of the right eye three months previously; the operated eye was enucleated, and the left eye recovered with a final visual acuity of 5-10. While all therapeutic procedures were used, massive doses of sodium salicylate appeared most effective. The literature on the treatment of this grave complication is reviewed. The course of these three cases suggests that enucleation of the exciting eye has a favorable effect on the process in the sympathizing eye.

Ray K. Daily.

Bonavolontà, G. **Statistical study of glaucoma observed at the eye clinic of Naples between 1936 and 1947.** Giorn. ital. oftal. **2**:108-121, March-April, 1949.

During the period 1936 to 1947 1,020 cases of glaucoma were observed. Among 139,900 patients examined at the clinic of the University of Naples during the years 1946 and 1947, an increased number, especially women, were afflicted with acute glaucoma. This was ascribed to the exceptional conditions of life during that time, and to increased emotional disturbances. The chronic glaucoma was found to be more prevalent in men. No acute glaucoma was found in persons less than 40 years of age and most of the cases occurred after 61. There is a relation between acute glaucoma and the vasomotor disturbances of the menopause.

Vito La Rocca.

Callahan, Alston. **A frequently-overlooked cause of blindness in infants: congenital glaucoma.** J. M. A. St. Alabama **19**:13-17, July, 1949.

Congenital glaucoma in infants should be considered when the eyes seem large. These infants sleep fretfully and hide their face from light. They have excessive lacrimation and rub their eyes frequently. The cornea stretches and becomes cloudy and the eyeball becomes large and is then a buphthalmus. The operative technique for goniotomy is described. Of ten children under the age of three years on which this operation was performed there were seven who had been followed for 6 to 12 months and in whom the glaucoma was cured. In another group, ranging in age from 3½ to 17 years there was only one successful operation of seven attempted. In the older age group the long continued pressure obliterates the canal of Schlemm and the spaces of Fontana. (10 figures, 1 table.)

H. C. Weinberg.

Löhlein, H. **Investigations on the angle of the anterior chamber in normal and glaucomatous eyes by means of Goldmann's gonioscope.** Wien, klin. Wchnschr **61**:698-702, Oct. 21, 1949.

Löhlein briefly reviews the history of gonioscopy. The technical difficulties have been largely overcome, but the nomenclature requires greater clarification, since histologic and gonioscopic terms have become confused. The author uses the Goldmann gonioscope. The patient, with induced miosis, is seated at the slit-lamp and a 30 fold magnification is used. By gradually turning the contact lens the examiner can see successively all parts

of the angle of the chamber, not all of them equally well.

The examination of 60 eyes in 40 persons without eye defects, ranging in age between 15 and 70 years, and in whom the refraction varied between +2.0 dptr. sph. and −6.0 dptr. sph., revealed that the angle of the chamber was wide in 16 subjects, moderately wide in 32 and narrow in 12. According to Troncoso's definition the angle of the chamber is wide when the band of the ciliary body is visible in its full width and the last ridge of the iris does not reach higher than up to the scleral spur. When the angle of the chamber is narrow the ciliary body either cannot be seen at all or it can be seen only between the high ridges of the iris. It cannot be said that the angle becomes narrower with increasing age. The author was unable to corroborate Barkan's observation that pigment accumulation increases with age; Löhlein found chamber angles free from pigment in all age groups. In emmetropic persons the angle was usually of moderate width, in the myopic it was wide or moderately wide and in the hyperopic it was narrow.

The author describes gonioscopic observations on 100 glaucomatous eyes in 65 patients. The studies were made under artificial miosis so as to better judge the possible presence of anterior peripheral synechias in the region of the angle of the chamber of the eye, that is, adhesions between iris and sclera. The site of the attachment of the iris, the thickness of the root of the iris, the position and thickness of the lens, the size of the ciliary processes, the strength of the ciliary muscle, the refractory status and other factors, taken all together, may influence the width of the chamber, although individually they may show no relationship to the width of the angle of the chamber.

Whatever type of gonioscopic classification is accepted for glaucomas, the following factors are of primary interest: 1. the width of the angle of the chamber, 2. the formation of synechia, 3. the degree of pigmentation of the trabeculum and 4. the sclerosis of the trabeculum. The author shows that the narrowing or obstruction of the angle of the anterior chamber and the degree of pigmentation of the trabeculum are of greatest interest. His examination of the angle of the chamber in 100 glaucomatous eyes revealed that when the eyes were divided into those with primary and secondary glaucoma, it was found that three-fourths of those with primary glaucoma had an open and one-fourth an obstructed angle, whereas among the 18 with secondary glaucoma 16 had an obstructed and only two an open angle. These and other observations reveal clearly a tendency to increasing contraction of the angle of the chamber in the course of chronic glaucoma, although during the primary stages the angle is open. This tendency became evident also in observations on 23 patients with bilateral chronic glaucoma simplex in which the degree of advancement of the disease differed in the two eyes. The author feels that the increasing contraction of the angle and the evidence of greater obstruction of the angle in the more severely diseased of the two eyes in the same patient justifies the conclusion that the obstruction of the angle of the chamber by synechia in patients with simple chronic glaucoma is secondary and not the cause of the increased pressures that occur during simple chronic glaucoma.

Studies on the pigment content of the angle of the chamber, in which a comparison was made between 54 normal eyes and an equal number with simple chronic glaucoma, revealed increased pigmentation in 20 percent of the patients with glaucoma and in 10 percent of those with normal eyes. This slight difference does not indicate that trabecular pigmentation has etiologic significance in the glaucomatous eye. The author feels that the ap-

pearance of anterior synechias and sudden intense pigmentations gives an unfavorable prognosis.

Theodore M. Shapira.

Soriano-Fischer, Elisa. **Twenty-eight cases of blindness caused by sympathetic ophthalmia.** Arch. Soc. oftal. hispano-am. **9**:850-860, Aug., 1949.

Among 2,917 cases of blindness which occurred between 1940 and 1949, Soriano found 28 caused by post-traumatic sympathetic ophthalmia. Their histories are briefly presented. Twelve were typical of sympathetic ophthalmia; in 16 the injured eye lost vision rapidly through optic atrophy or papillitis, so-called posterior ophthalmia. The rapid loss of vision is contrary to the general belief that posterior ophthalmia runs a slow and protracted course, and that enucleation of the injured eye is more beneficial here than in typical sympathetic ophthalmia. The author makes a plea for early enucleation of all injured sightless eyes.

Ray K. Daily.

Thomassen, T. L. **The glass rod test in glaucomatous eyes.** Brit. J. Ophth. **33**: 773-778, Dec., 1949.

It has been reported that the glass rod test varied with the height of the ocular tension and with the phase of oscillation but was not invariably negative in glaucoma. When the bulbar tension was in an increasing phase, the test was never positive, that is, the aqueous did not replace the blood in the recipient vein so that it entered the vein previously filled with blood. When the bulbar tension was in a decreasing phase this test was sometimes found to be positive even when the ocular tension was increased. It did not seem to matter whether the decreasing phase was spontaneous or produced by pilocarpine. When the tension remained on a steady, but increased level, the test was usually negative but in a few cases it was positive in spite of a markedly increased tension. Repeated examinations of the same aqueous vein often gave very different results. After a discussion of the formation and production of aqueous humour, the author concludes that the cause of the phenomena in glaucomatous eyes must be sought in the blood veins. Venous pressure is high in proportion to the bulbar tension when the latter is in an increasing phase and this tends to cause a negative glass rod test. When the bulbar pressure is in a decreasing stage, however, the venous pressure is low compared to the bulbar pressure which tends to make the test positive.

Orwyn H. Ellis.

10

CRYSTALLINE LENS

Cogan, D. G., Martin, S. F., and Kimura, S. J. **Atom bomb cataracts.** Science **110**:654-655, Dec. 16, 1949.

Ten subjects between the ages of 13 and 55 years who were 550 to 950 meters from the hypocenter at the time of the atomic bomb explosions showed similar types of cataracts. In both eyes there were opacities of the posterior lenticular capsules in an area of 2 to 4 mm. in diameter in the axial zone, with occasional punctate opacities toward the periphery. The doughnut-shaped opacities were sharply defined with jagged edges and light centers. Slitlamp examination showed the cataracts to be lace-like in texture with a few polychromatic crystals and a few vacuoles in the posterior capsule with no extension to the underlying cortex, although the vacuoles were just in front of the capsule. The anterior capsule showed a few puncta in seven patients with an occasional vacuole in three of them. The cataracts are similar to those associated with exposure to X rays and gamma rays. The part played by the neutrons in the pathogenesis of these lens opacities was not evident. H. C. Weinberg.

Fuentes Noya, M. **Treatment of secondary membranous cataract.** Arch. Soc. oftal. hispano-am. **9**:1014-1018, Sept., 1949.

Fuentes advocates complete extraction of a membranous cataract, which he achieves through one limbal incision, and the use of a specially designed hook. At one end this instrument has the usual iris hook, and at the other an S-shaped hook. The iris hook is introduced through the incision, and carried across the anterior chamber, where it separates the membrane from the iris; it is then withdrawn, and the S-shaped hook introduced; by manipulating this hook the entire membrane is caught within its grasp; by twisting it the membrane is separated from its attachment and made free in the anterior chamber. It is then withdrawn on the hook. (14 figures.)

Ray K. Daily.

Gerber, Hans. **Penicillin prophylaxis in operations for cataract.** Wien. klin. Wchnschr. **61**:685-686, Oct., 21, 1949.

Gerber says that postoperative infection and expulsive hemorrhage are the most serious complications of operations for cataract, which sometimes may result in the loss of an eye. He cites figures on the incidence of postoperative infections before the prophylactic use of penicillin was a routine measure in patients to be operated on for cataract. He also briefly describes four case histories of patients who were treated with penicillin for postoperative infection. These histories show that although from two to five million units of penicillin are required for the treatment of postoperative infections, this treatment does not necessarily preserve the function of the eye. On the other hand the prophylactic treatment with penicillin requires comparatively small quantities and no postoperative infection was observed in the 242 cataract operations in which prophylactic penicillin was employed routinely.

Theodore M. Shapira.

Penido Burnier, J., and Souza Queiroz, L. **Congenital cataract secondary to maternal rubeola during pregnancy.** Arq. do Instituto Penido Burnier **8**:94-103, June 1, 1949.

The authors' first patient, nine years of age, had unilateral microphthalmia, cataract, and mitral stenosis. The second patient, six years of age, had bilateral microphthalmia and cataract. Both mothers had had rubeola during the first month of pregnancy. It is the authors' belief that soft cataracts should be operated upon by corneal incision with the keratome, wide capsulectomy, and curettage or aspiration of the lens substance.

W. H. Crisp.

Smith, F. W. G. **Extraction of cataract in a case of sympathetic ophthalmia.** Brit. J. Ophth. **33**:779-780, Dec., 1949.

A case of cataract extraction following sympathetic ophthalmia is reported. Inserting two Ziegler needles into the lens substance facilitates its delivery. It is suggested that where cataract has developed after sympathetic ophthalmia fairly early operation might be undertaken, as the iridocapsular membrane is softer if undue inflammation is not present and the acute recurrences have subsided.

Orwyn H. Ellis.

11

RETINA AND VITREOUS

Böck, J. **Relation between areas of shrinkage in the detached retina and the vitreous.** Wien. klin. Wchnschr. **61**:672-675, Oct. 21, 1949.

Böck concerns himself particularly with the folds that are observed when detachment of the retina exists. He says

that Gonin, who laid the foundations for the modern treatment for detachment of the retina gave considerable attention to these pleats or folds, dividing them into two types, star-shaped folds ("plis étoilés") and radiating folds ("plis irradiants"). Gonin believed that the radiating folds developed only after operative interventions, particularly after penetrating ignipuncture. These radiating folds, which apparently branch outward from the field of operation have also been observed and discussed by others, among them Meller, who regarded them as a bad result of ignipuncture and indicative of an unfavorable result. Gonin was of the opinion that at the site of the burn resulting from the ignipuncture, the retina and vitreous become fused. The shrinkage of the cicatricial tissue gives rise to the formation of folds. Other observers, among them Vogt, expressed similar opinions.

The star-shaped folds in contradistinction to the radiating folds are observed not only after interventions but also before. They are not necessarily restricted to the disturbed area, but may appear distant from it. Radiating folds do not necessarily signify an unfavorable prognosis, the star-shaped folds always do. Gonin and others stress this.

Gonin believed these star-shaped folds to be the result of adhesions between vitreous and retina. Böck describes investigations on the relationship between the vitreous and these star-shaped areas of shrinkage by Lindner's methods of investigating the posterior vitreous with the slitlamp and corneal microscope. They were facilitated by using the binocular microscope with Goldmann's improved slitlamp and Hruby's anteriorly placed filter.

The author points out that contrary to Gonin the areas of retinal shrinkage (folds) are not due to adhesions between vitreous and retina, but to detachment, and to the presence of subvitreal fluid between vitreous and retina. This was supported by histologic observations in the presence of retinal detachment. Leber's second theory of the origin of retinal detachment as the result of the development of a cellular membrane on the surface of the retina following preretinitis suggests that such changes develop only at sites where the vitreous is no longer attached to the retina. Böck presents two case histories which demonstrate that in the presence of favorable conditions the slitlamp will show that vitreous and retina are detached in the areas of shrinkage. Theodore M. Shapira.

Busacca, Archimede. **Observations on a form of chorioretinitis with retinal detachment.** Arch. d'opht. **9**:549-583, 1949.

Busacca describes a form of chorioretinitis which attacks young subjects selectively in the region of the posterior pole. It starts as an inflammatory and necrotic focus which soon leads to a retinal separation, most often situated near the papilla and extending between the upper and lower temporal vessels. The disc is not usually clinically involved in the process, but there may be perivascular infiltraton of the vessels of the disc and exudation into the vitreous. Perimetry reveals almost constantly a sector defect. In the majority of cases the retina reattaches spontaneously and the patient regains good vision, but in a significant percentage of cases the vision remains permanently low. The healed focus is always ophthalmoscopically prominent and the vitreous opacities tend to be persistent. Busacca differentiates the lesion sharply from the juxtapapillary chorioretinitis of Jensen. He considers the etiology unknown. He reports on the pathology of one case and states that the lesion is primarily cho-

roidal and not retinal. For treatment he considers the following to be of value: sodium salicylate intravenously, sodium hyposulfite intravenously, fever therapy, and roentgentherapy according to the technique of Mattey, Jeandelize, and Gault (Bull. Soc. Opht., Paris, 1934).

Phillips Thygeson.

Duguet, J., Dumont, P., and Bailliart, J. P. **The effects of anoxia on retinal vessels and retinal arterial pressure.** J. Aviation Med. 18:516-520, Dec., 1947.

The retinal vessels were studied because changes in them reflect the changes in the local circulation produced by high altitudes and also, by analogy, they reflect the changes which occur in the circulation in the deep vessels in the brain. The enlargement of the retinal vessels is great enough to be measured at 4,000 meters and reaches its maximum at 6,000 meters. The retinal arteries become darker and approach the color of the veins. The rich branching of the arteries near the macula becomes apparent. The general color of the retina is darker and the disc loses its pale rose color and becomes light bluish gray. This discoloration is concomitant with the general cyanosis due to a decrease in the oxyhemoglobin percentage in the blood. The retinal veins also become dilated. In anoxia there is an increase in retinal arterial pressure as well as a general rise in blood pressure. This decreases slowly with the duration of exposure to the anoxia of high altitudes. There is a fall in retinal arterial pressure in anoxia in individuals who cannot tolerate the high altitudes. (3 figures.) H. C. Weinberg.

Fanta, H. **Hypotension in the vessels of the area of the central retinal artery.** Wien. klin. Wchnschr. 61:679-681, Oct. 21, 1949.

In Fanta's clinic the examination of patients with headache includes a measurement of the pressure in the central retinal artery and hypotension was noted in a considerable number of patients. Some of the patients had hypotension in the general blood pressure and a corresponding hypotension in the region of the central artery of the retina. They complained not only of headaches but also of visual disturbances. Some also had vertigo. Visual acuity and the eyeground were normal. Their symptoms improved after treatment with caffeine and "sympatol."

In another group of patients there was no hypotension in the general circulation, but measurement of the pressure in the central retinal artery revealed isolated hypotension in the region of the cerebral vessels. These patients were of greater interest to the ophthalmologist. They complained of headache and intermittent visual disturbances, and were free from refractive errors and heterophoria. In one of them with almost intolerable headache the ratios of systolic and diastolic pressures in the brachial and in the retinal artery were 125/95 and 45/23, respectively. After his nicotine poisoning had subsided the ratios became more nearly normal and he was comfortable.

After citing observations on several other patients, the author says that absolute isolated hypotension in the region of the central retinal artery has been observed in patients with essential epilepsy, Parkinson's disease, postencephalitis conditions, multiple sclerosis, traumatic encephalopathia, neurosympathetic dystonia, involutional psychoses, dementia praecox, chronic alcoholism, progressive paralysis, myocarditis, myocardial malacia, cardiac insufficiency, endocarditis, pernicious anemia, lymphogranulomatosis and tuberculosis. Lauber suggested that hypotension in the region of the central retinal artery might be the cause of atrophy of the optic nerve in tabes. Pseudoglaucoma likewise has been ascribed to it.

The patients whose histories are reviewed here by Fanta complained chiefly of headache and visual disturbances, vertigo was often admitted only on questioning. It is noteworthy that many of these patients found their condition easier to bear when reclining. They never exhibited pathologic conditions in the eyeground. Theodore M. Shapira.

Godtfredsen, Erik. **Investigations into pyaluronic acid and hyaluronidase in the subretinal fluid in retinal detachment, partly due to ruptures and partly secondary to malignant choroidal melanoma. Preliminary report suggesting a new hypothesis concerning the pathogenesis of retinal detachment.** Brit. J. Ophth. 33.721-732, Dec., 1949.

The presence of hyaluronic acid and hyaluronidase in the subretinal fluid was investigated as a possible contribution to the pathogenesis of retinal detachment. The literature regarding the nature of the vitreous and the subretinal fluid is reviewed. Within a skin area it has been shown that the allergic tissue reaction will involve the local production of hyaluronidase, which, by its influence on the hyaluronic acid of the connective tissue, contributed to the allergic process. This hyaluronidase activity may be inhibited by antihistamines.

Investigations on 17 patient with all degrees of retinal detachment are reported. At the time of operation the subretinal fluid flowing through the scleral perforations was collected and subsequently tested by the viscosimetric technique. Large amounts of hyaluronic acid were present in all cases of primary serous retinal detachment with scleral rupture. This bears out the hypothesis that the subretinal fluid comes from the vitreous, the considerable hyaluronic acid content of which has been established. The hyaluronic acid concentration in the subretinal fluid is small at first, then later gradually increases. Hyaluronic acid was absent in the subretinal fluid of both cases of malignant choroidal melanoma examined.

The author presents a new hypothesis concerning the pathogenesis of retinal detachment. The development takes place gradually by a primary angioneurotic retinal ischemia followed by necrosis, producing a cystoid degeneration, then rupture and an associated partial liquefaction of the vitreous body. The liquefaction is caused by local liberation of hyaluronidase which in turn produces partial depolymerisation of the hyaluronic acid in the vitreous body. The inactivation of the hyaluronic acid by antihistamines suggests a possible supplementary treatment. It is possible that tests for hyaluronic acid may become important in the differential diagnosis in cases of primary and secondary retinal detachment.

Orwyn H. Ellis.

Hruby, K. **New clinical aspects of ophthalmology.** Wien. klin. Wchnschr. **61** : 693-695, Oct. 21, 1949.

Posterior detachment of the vitreous body, i.e., the detachment and retraction of the vitreous body from the portion of the retina which is situated behind the ora serrata is frequently or regularly associated with axial myopia, the senium, inflammations of the uvea, blunt or perforating injuries of the eyeball, hemorrhages in the vitreous space, detachment of retina and other diseases of the eye. Gliosis-like densifications in the detached posterior limiting layer of the vitreous body, which may appear on ophthalmoscopic examination, as "formed opacity of the vitreous," may be a guiding symptom. In the absence of this symptom, the slitlamp will be an aid in diagnosis. The opacities are observed by the patient as "flying spots" because their shadows on the retina are perceived entoptically. The detachment of the vitreous body may be

associated with photopsia. No effective treatment is available, but the condition as a rule is benign except for the very rare occurrence of retinal tear.

Chorioretinitis centralis serosa (Kitahara's disease) has been described particularly by Japanese authors. Examination of the eyeground with the slitlamp facilitates the diagnosis. The disease may be considered as a circular circumscribed serous detachment of the retina in the area of the macula with more or less pronounced edematous infiltration of the flatly detached retina itself. The cause of the serous retinal detachment is a circumscribed, inflamed focus in the choroid which as a rule becomes ophthalmoscopically visible in the course of the disease. The disease has a predilection for patients of medium age and is characterized by a disc-like positive scotoma. Subretinal effusion and edema of the retina become adsorbed within two to three months. The prognosis is favorable. Local recurrences may be observed. Treatment is of little avail.

Coats's retinitis exudativa externa of the macula starts with a sudden visual disturbance caused by a yellow or gray, round, slightly elevated, inflamed focus in the macula or adjacent to it, with hemorrhages in the outermost layers of the retina. Changes may be localized in the deepest layers of the retina with the aid of the slitlamp and thus the name of the disease seems to be justified. The disease has a chronic course. The exudate will never be adsorbed completely and a yellow-whitish central induration may develop. An improvement of the visual acuity, therefore, is only possible with a paracentral localization of the disease. The disease has a predilection for the young. According to Rieger, Coats's retinitis may be considered as an embolic tuberculous, vascular disease of the center of the retina, but coccal embolism in the capillary net of the retina may be its cause. Short fever therapy by milk injections followed by tuberculin therapy is recommended.

Kreibig's opticomalacia is an acute nutritional disturbance with a focus of softening in the optic nerve between chiasm and papilla, due to severe sclerotic changes of the vessels which supply this portion of the optic nerve. The diagnosis can only be made by exclusion or ex juvantibus. The advanced age of the patient, a general and local arteriosclerosis, the severe acute visual disturbance with little changes in the papilla, and the complete absence of pain offer valuable indications for the nature of the condition. Practical or real blindness of the diseased eye cannot be prevented by fever therapy or other procedures.

Primary (symmetric) cleft of the retina is the term suggested by the author for a well characterized syndrome which may be diagnosed frequently when refracting or examining the eyeground. The fundus presents the aspect of a circumscribed, high, vesicular or limited flat "detachment of the retina," which is characterized by the transparence of the thin, detached retina, the absence of any folds or grooves, the absence of visible defects of the retina, and in most instances the absence of posterior detachment of the vitreous body. The symmetry facilitates the diagnosis but it is possible that the cleft of the retina may be high and markedly cystic on one side, while it may be still quite flat on the opposite side. The ophthalmoscopic picture of a "detached retina" is to be considered only as a "simulated detachment," which results from the detachment of the inner layers of the retina, while the outer layer of the retina still adheres to the bulbar wall. True detachment as a sequel of a cleft retina can be considered only after perforation of both the layers of the retina, possibly after perforation of the outer layer alone and when the retina is torn

from the ora serrata because of traction associated with progressive cystic extension. Primary cleft of the retina always was observed by the author in the temporal half of the retina. The cystoid degeneration induces a cleft only in a biologically young retina.

Spontaneous regression of cleft-cysts of the retina was observed as a result of rupture of the wall of the cyst. Surgery is therefore not advisable in the early stages of primary clift of the retina but in instances with a progressive course is more promising than in cases of true detachment. Surgical treatment consists of isolating the cleft-cyst by means of diathermal puncturing.

The progress which has been achieved in ophthalmologic diagnosis during the last 30 years is partly a result of the introduction of slitlamp-microscopy of the eyeground. Theodore M. Shapira.

NEWS ITEMS

Edited by Donald J. Lyle, M.D.
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News items should reach the editor by the 12th of the month but, to receive adequate publicity, notices of postgraduate courses, meetings, and so forth should be received by the editor at least three months before the date of occurrence.

Deaths

Dr. Samuel Abraham Durr, San Diego, California, died December 4, 1949, aged 55 years.

Dr. Emory Edward Holland, Richmond, Indiana, died October 13, 1949, aged 65 years.

Dr. Eugene Ezra Neff, Madison, Wisconsin, died October 31, 1949, aged 59 years.

Miscellaneous

Receives research grant

The department of ophthalmology in the University of Toronto has received a grant from the Ontario Provincial Department of Health through funds provided by federal grants for research work on the prevention of blindness from glaucoma. This work will be done under the direction of Dr. T. H. Hodgson in the Banting Institute, Toronto General Hospital, and other university teaching hospitals in Toronto. The initial grant was $8,200. It is proposed that the research work will extend over 3 to 5 years.

Announcements

Orthoptic examinations

The annual examination of orthoptic technicians by the American Orthoptic Council will be conducted in September and October, 1950.

The written examination will be nonassembled and will take place on Thursday, September 7, in certain assigned cities and offices and will be proctored by designated ophthalmologists.

The oral and practical examinations will be on Saturday, October 7, in Chicago, just preceding the meeting of the American Association of Orthoptic Technicians.

Application for examination will be received by the office of the secretary of the American Orthoptic Council, Dr. Frank D. Costenbader, 1605 22nd Street, N.W., Washington 8, D.C., and must be accompanied by the examination fee of $25. Applications will not be accepted after July 1, 1950.

Council for children

The International Council for Exceptional Children will hold its annual meeting at the Stevens Hotel, Chicago, March 19 to 23. The problems of handicapped children, including those who are blind or partially sighted, will be the subject of the conference.

Glasgow meetings

Each Wednesday evening during March a series of meetings will be held in the department of ophthalmology, University of Glasgow, at eight o'clock.

On March 1, Dr. D. Christison will speak on "Prognosis in iridocyclitis;" on March 8, Dr. S. Galbraith, "The evolution of the ophthalmoscope;" on March 15, Dr. J. D. Fraser, "Glioma of the retina;" on March 22, Dr. T. D. M. Roberts, "Primary visual receptors;" and on March 29, Dr. T. Wilson, "Modern methods of investigation."

Following the presentation of the main paper, the meetings will be open for discussions.

Societies

Eastern research program

The Eastern Section of the Association for Research in Ophthalmology met at Lenox Hill Hospital, New York, on January 28. Papers presented at this meeting were:

"Cytological and bacteriological studies on the aqueous humor in uveitis," Dr. John Locke; "Experimental tissue therapy in selected ophthalmological disorders," Dr. Ervin Tusak; "Alkali

resistant polysaccharides of the retina," Dr. Frederick Williams; "Synthesis of glutathione in normal and cataractous lens," Dr. Frederick Merriam and Dr. V. E. Kinsey; "Reduction of visual acuity resulting from exposure to sunlight," Dr. R. H. Peckman and Dr. R. D. Harley; "Choline acetylase activity in ocular tissues," Dr. Andrew de Roetth; "Clinical and experimental observations of cycloelectrolysis and cyclodiathermy," Dr. Arthur B. Duel, Jr., and "Studies in ACTH in eye diseases," Dr. John McLean and Dr. Daniel Gordon.

Pennsylvania Academy meeting

The annual meeting of the Pennsylvania Academy of Ophthalmology and Otolaryngology will be held May 12, 13, and 14, 1950, at the Bedford Springs Hotel, Bedford, Pennsylvania.

Among the speakers who will present papers at this meeting will be: Dr. Edward H. Campbell, Dr. Frank D. Costenbader, Dr. Karl Houser, Dr. Raymond E. Jordan, Dr. John E. L. Keyes, Dr. John A. Kolmer, Dr. Francis L. Lederer, Dr. Irving H. Leopold, Dr. Maurice Saltzman, Dr. Richard G. Scobee, Dr. Edmund B. Spaeth, and Dr. Frank B. Walsh.

In addition to the formal presentations, 12 study clubs will be conducted. There will also be an open forum, an "information please" type of session, on the topics "Refraction difficulties in presbyopia," and "Common office procedures in Otorhinolaryngology."

Officers of the Pennsylvania society are: President, Dr. Daniel S. DeStio, Pittsburgh; president-elect, Dr. Jay G. Lim, Pittsburgh; secretary, Dr. Benjamin F. Souders, Reading.

East-Central section

The East-Central Section of the Association for Research in Ophthalmology met at the Hotel Statler, Cleveland, Ohio, January 10. The evening meeting was with the Cleveland Ophthalmological Club. Dr. Harold Scheie was the guest speaker.

The program was: "Hyaluronidase: An aid to local anesthesia in ophthalmology," Dr. Harvey E. Thorpe; "The efficiency of local anesthetics when used in small doses," Dr. H. S. Hamilton, and Dr. J. F. Aikenhead; "Acetyldimethylbenzylammonium chloride: A new ophthalmic irrigating solution," Dr. Richard P. Bell, Jr., and Dr. Lorand V. Johnson; "The effects of glove powders on the eye," Dr. Frank E. Schwartz and Dr. Jay G. Linn, Jr.; "Galactosemic cataract," Dr. Harold F. Falls; "Aureomycin as ophthalmia neonatorum prophylaxis," Dr. Samuel G. Clark and Dr. Arthur M. Culler; "Studies of toxoplasma in tissue cultures," Mr. T. Suie, Jr., Dr. Jackson W. Riddle, and Dr. Arthur M. Culler; "Protein transport in ocular structures," Dr. Albert M. Potts, Dr. Lorand V. Johnson, Miss Mildred Orchen, and Miss Doris Goodman; "Effect of anticonvulsant drugs on retinal metabolism," Dr. Anita P. Gilger, Dr. Albert M. Potts, and Dr. Lorand V. Johnson; "Aqueous veins and refraction-correcting contact lens," Dr. K. W. Ascher; "Beta-ray applicators: A comparison of several types of beta-radiation sources," Dr. H. L. Friedell; "A new method for measuring aniseikonia," Dr. G. A. Brecher; "Effect of staphylococcus growth products on a flavoenzyme system," Mr. Robert C. Nelson and Dr. Lorand V. Johnson; and "Greater superficial petrosal neurectomy for the relief of chronic bullous keratitis," Dr. Lorand V. Johnson and Dr. William A. Nosick.

Officers of Richmond society

The Richmond, Virginia, Eye, Ear, Nose, and Throat Society has elected the following officers: President, Dr. E. W. Perkins; secretary, Dr. J. Warren Montague. The society meets at the Commonwealth Club on the first Tuesday of January, March, May, and October.

Milwaukee program

At the January 24 meeting of the Milwaukee Oto-Ophthalmic Society, Dr. H. Isabelle McGarry of the Illinois Eye and Ear Infirmary, Chicago, presented a paper on "Management of the glaucoma clinic," which was discussed by Dr. E. E. Grossmann. Dr. George Dunker is president of the society; Dr. B. P. Churchill, secretary.

Los Angeles officers

Recently elected officers of the Los Angeles Society of Ophthalmology and Otolaryngology are: President, Dr. Alden H. Miller; secretary-treasurer, Dr. Victor Goodhill. Section on Ophthalmology: Chairman, Dr. Dennis V. Smith; secretary, Dr. Carroll McCoy. Section on Otolaryngology: Chairman, Dr. Howard P. House; secretary, Dr. J. Edwin Scobee. Meetings are held at 6 P.M. at the Los Angeles County Medical Association Building, 1925 Wilshire Boulevard, on the fourth Monday of each month from September through May.

Brooklyn program

During the instruction session at the 111th regular meeting of the Brooklyn Ophthalmological Society, Dr. Harold F. Schilback spoke on "Technique of conducting perimetry and angioscotometry."

Papers of the evening were: "Therapeutics with antibiotics," by Dr. Alson E. Braley, and "Glaucoma," by Dr. Daniel Kravitz, with a discussion by Dr. Willis S. Knighton.

PRESCRIPTION OPTICIANS

POSTGRADUATE CONFERENCE IN OPHTHALMOLOGY, UNIVERSITY OF MICHIGAN MEDICAL SCHOOL—The Department of Postgraduate Medicine of the University of Michigan Medical School announces the annual conference in Ophthalmology for qualified physicians, April 24, 25 and 26, 1950, to be given at the Horace H. Rackham Graduate School Building, Ann Arbor, Michigan, under the direction of the Department of Ophthalmology, at the University of Michigan. Guest Lecturers: Dr. John B. Hitz, Milwaukee; Dr. Herman Elwyn, New York City; Dr. Albert E. Sloane, Boston; Dr. Paul L. Cusick, Detroit; and Dr. Kenneth C. Swan, Portland. Resident Lecturers: Dr. F. Bruce Fralick, Dr. Harold F. Falls, Dr. John W. Henderson.

Complete program and details will be mailed upon request addressed to Dr Howard H. Cummings, Chairman, Department of Postgraduate Medicine, University Hospital, Ann Arbor, Michigan.

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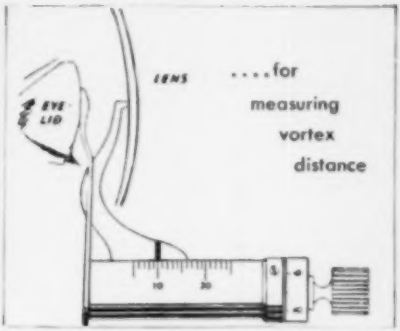

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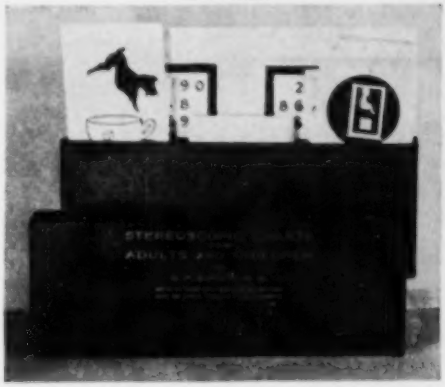

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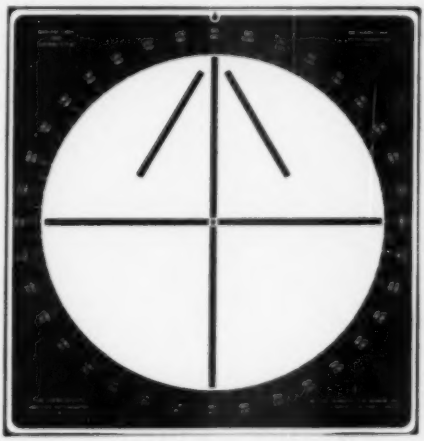

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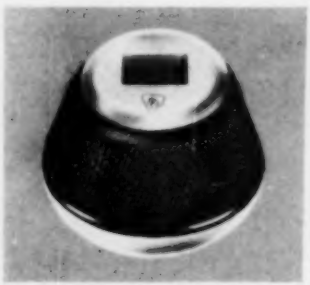

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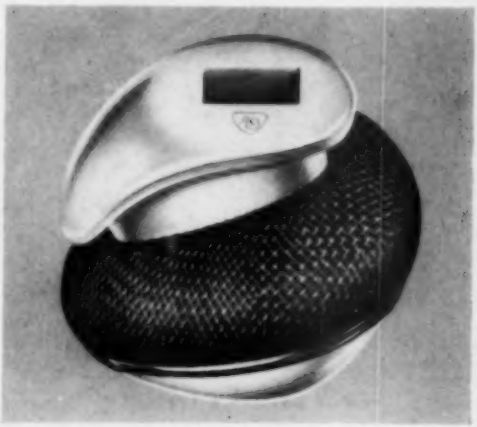

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VOLUME 33 NUMBER 3, PART II MARCH, 1950

AMERICAN JOURNAL
OF
OPHTHALMOLOGY

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The

INTERNATIONAL SYMPOSIUM

on

CORNEAL SURGERY

sponsored by

THE EYE-BANK FOR SIGHT RESTORATION, INC.

April 19 and 20, 1949

at the

Manhattan Eye, Ear and Throat Hospital

New York

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For complete table of contents see page one

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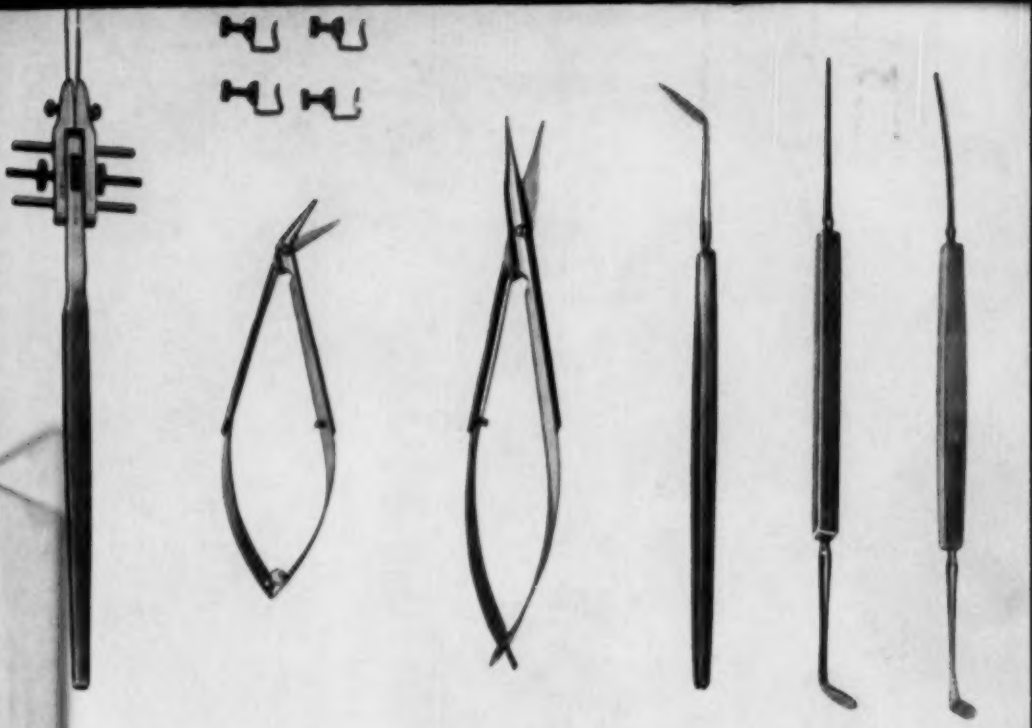

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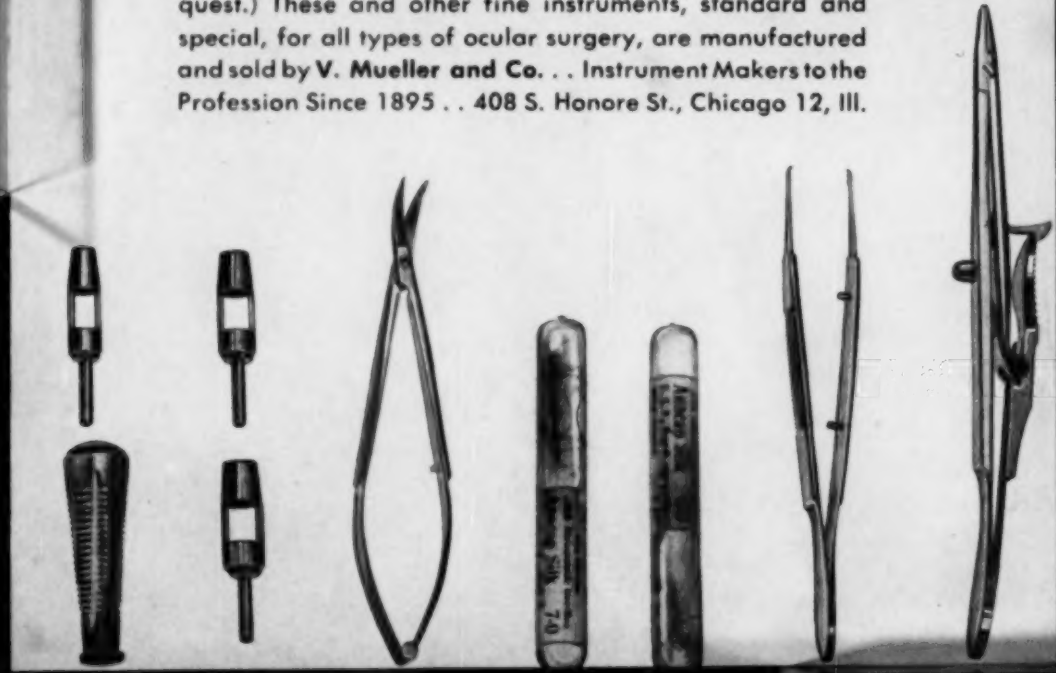

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and the

INTERNATIONAL SYMPOSIUM ON CORNEAL SURGERY

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The Eye-Bank for Sight Restoration, Inc.
New York, April 19 and 20, 1949

CONTENTS

More than a Surgical Strand...
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AMERICAN JOURNAL OF OPHTHALMOLOGY

VOLUME 33 MARCH, 1950 NUMBER 3, PART II

and the

International Symposium on Corneal Surgery

FOREWORD

R. TOWNLEY PATON, M.D.
New York

The Eye-Bank for Sight Restoration, Inc., now completing its fourth year, was established primarily to provide a constant supply of suitable eyes to qualified surgeons capable of performing the corneal grafting operation wherever and whenever needed. The supply, though not adequate, has already exceeded 1,200 eyes which have been received and supplied free of charge to the surgeon.

The Eye-Bank staff has taught the technique of the operation to many young ophthalmologists who came here on fellowships upon discharge from military service. It will continue to offer courses in technique to surgeons who need and seek them. In addition, experimental work related to corneal surgery, both of a clinical and of a more basic interest, has been conducted by the Eye-Bank throughout these four years.

A concentrated effort, such as here envisioned, to study blindness as a result of damage to the cornea growing out of injury or disease has never before been attempted. Because of the increasing interest in this subject and the advances which have been made in corneal surgery, this International Symposium has been organized in the conviction that an exchange of knowledge on research problems involved in keratoplasty by those working in this field will advance the service of ophthalmology in the alleviation of blindness throughout the world.

Grateful acknowledgement is expressed to Mrs. Aida Breckinridge, executive director of the Eye-Bank, for her efforts in making possible the International Symposium on Corneal Surgery.

CORNEAL TRANSPLANTATION: A HISTORICAL REVIEW

R. TOWNLEY PATON, M.D.
New York

Time is too limited to give a complete historical review of corneal transplantation but it may be of interest to touch upon some of the highlights in the history of its development.

The earliest attempt to construct an artificial cornea, substitute a scarred cornea, was made in 1789 by Pellier de Quengsy, who suggested to the Montpellier faculty that a piece of glass similar to the crystal on a watch be introduced after removal of completely opaque leukoma. Thus was born the idea of creating an artificial cornea; an idea that was not destined to meet with success, although experiments in this direction are still being made in our day.

In 1814, Autenrieth suggested replacing the opaque cornea by an artificial pupil

opening in the sclera of the eye. An artificial pupil seemed to be much more practical than keratoplasty. There were repeated attempts to restore the function of sight by opening a window in the sclera (Schmidt, 1814; Beer, 1814; Himly, 1818; Gertner, 1817; Riecke, 1823; and others). However, none of these operations appeared to be successful, for the scleral aperture was soon closed by the formation of a membrane.

The real origin of keratoplasty can be traced back to Meissner's idea of closing the scleral window with a transplanted animal cornea. All attempts in this direction proved unsuccessful, however, and in his dissertation on the formation of an artificial pupil in the sclera in 1823, Meissner reported unfavorably on the possibility of transplanting the cornea.

The failure of Meissner's attempts led to the thought of other possibilities, among which, naturally, was that of transplanting the cornea, not to the scleral opening, but in place of the removed leukoma itself.

Reisinger is usually given credit for this, although priority was disputed by Himly who wrote: "I was the first to suggest in my lectures years ago the replacement of an opaque cornea by foreign transplant cornea; and am therefore surprised that my pupil and friend, Reisinger, who heard me express this idea in 1813, should claim it as his own in 1818. My experiments of transplanting the cornea of a rabbit to the eye of another rabbit, and from a rabbit to a cat, were successful in so far as the transplants 'took'; however, they became opaque in from three to four weeks."

Be this as it may, Reisinger attempted the almost complete resection of a rabbit's cornea, leaving it only attached by a thin pedicle. He obtained good healing, but the cornea became opaque. After this, Reisinger performed total resections of the cornea, and then put the latter back in place, without any sutures; the cornea took well, but lost its transparency. Reisinger named this operation "keratoplasty."

Reisinger's work, reported in 1824, failed to attract the attention it merited, and was not favorably received. The general attitude toward keratoplasty in those days was well expressed by Dieffenbach who, in 1831, made the following statement: "Reisinger's idea of replacing an opaque human cornea by the cornea of an animal was one of the most daring fantasies if this operation could be successful. This would be in itself the highest recompense."

There were many experiments carried on between 1833 and 1836. It was Stilling who in that year suggested transplanting, not the entire cornea, but only a piece of it, corresponding to the pupil in size. He advocated fitting the transplant to the exact size of the window so as to prevent the escape of the aqueous humor, and also suggested that it be drained by creating a fistula in the lower part of the limbus.

Koenigshoefer suggested the use of a double-bladed knife (two Beer's knives joined together) for keratoplasty; thus, transplants and windows of exactly the same size could be obtained. He was also the first to attempt using a cadaver transplant.

Strauch apparently was the first Russian physician to do experimental keratoplasty, in 1841. Strauch operated on rabbits and obtained good results, but he did not follow-up the animals for sufficiently long periods.

In that same year, Markus published the results of his experiments in transplantation of the cornea. He was the first to formulate the conditions necessary for a successful operation. An excellent account may be found in the *American Encyclopedia of Ophthalmology*.

Steinberg, in 1843, proposed a trephine-shaped instrument, eight mm. in diameter, fitted with four spears that (in his opinion) would give exact coincidence in shape and size between transplant and window. This instrument was rather complicated and its use demanded considerable dexterity, but the inventor claimed that the spears penetrated well into the cornea, thus immobiliz-

ing the eyeball, and that the incisions they left facilitated suturing. Steinberg excised the transplant with his instrument, then, placing the fragment on a cork-plate, drew four sutures through it. The window in the host's cornea was next excised, and the transplant placed into the window, the sutures in it being easily passed through the incisions left by the blades and tied. Steinberg used this method in operating on 12 rabbits, but only obtained healing in one case; even this transplant became opaque.

In 1877, Von Hippel published his work entitled "On the operative treatment of total leukomas." He advanced the technique of keratoplasty considerably, and his trephine is still in use today. Because of Von Hippel's trephine, partial transplantation became used more and more widely, and gradually began to take the place of total transplantation. He experimented with both the penetrating and nonpenetrating types of transplantation. He performed many operations on humans, using both the heteroplasty and homoplasty methods, but the successful cases were usually those in which he used nonpenetrating keratoplasty. The transplanted cornea retained transparency in some cases for weeks, in others for months, and the vision of many patients improved to being able to distinguish large objects, and to orientate themselves in space. Von Hippel considered keratoplasty to be a not-at-all dangerous operation and recommended its use in all cases of total leukoma.

From then until 1907, numerous experiments were made and many successful and unsuccessful cases were reported. It was in 1907 that Zirm, the Austrian physician, reported his famous case on which he had operated in 1905, and which was to receive world-wide attention.

Zirm had operated on both eyes of a man with leukomas caused by lime burn; he performed transplantations, using the partial penetrating method and utilizing the cornea from the enucleated eye of an 11-year-old boy. Soon after the operation, the right eye was lost because of secondary glaucoma, but the transplant in the left eye remained smooth and transparent, with vision of 0.1. Thus the patient could read and write again. Unfortunately, the patient died three years later from an accidental infection.

After Zirm, many research workers devoted themselves to kertoplasty with renewed interest.

Perhaps the best known and remembered work of this period is that of Elschnig of Prague, who began to use keratoplasty extensively from 1908 on. From 1908 to 1930, 203 corneal transplantations were performed at the Prague Clinic, the average incidence of transparent healing being 20 percent. In leukomas following interstitial keratitis, the percentage of transparent takes was 73 percent.

However, even in the hands of Elschnig, the percentage of complications was fairly high. According to Elschnig's figures, the transplant was lost in 22 cases out of 139. In 1914 Elschnig demonstrated a number of patients with transplants that had remained transparent over a long period of time.

It is not exactly clear as to when Filatov started performing keratoplasties, but in 1922 he published some good results. In 1938, his clinic had done 436 transplantations of the cornea. In most of these cases, eyes from living subjects were used; subsequently, however, it is reported that he preferred using the eyes of cadavers. Filatov made several important contributions to this field of surgery. He perfected the spatula to be used to prevent any injury to the lens or prolapse of the vitreous during the operation.

Those interested in this field of surgery are well acquainted with the present trends. Perhaps the most interesting development, and in this country the least known, is the use of the nonpenetrating corneal transplant for therapeutic purposes. The French school of surgeons has been largely responsible for this development. Up-to-date statistics are meager, but the results are encouraging.

TECHNIQUE OF PENETRATING KERATOPLASTY

J. I. Barraquer, Jr., M.D.
Barcelona, Spain

Excepting the complications which result when a contraindicated keratoplasty is performed and those arising in the cases already classified as unfavorable, postoperative complications are usually due to poor coaptation of the graft caused by (1) defective cut resulting in the irregular shape of the trephination or the graft; (2) faulty fixation; and (3) differences in thickness between the two corneas.

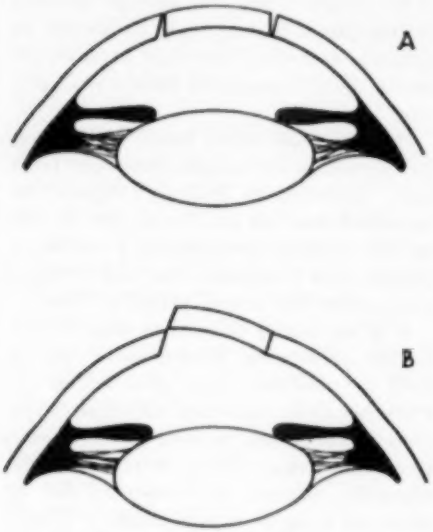

Fig. 1. (Barraquer). (A) Defective coaptation because of oblique cut. (B) Displacement of graft (shown in A) is favored by normal intraocular pressure and oblique cut when the fixation is no longer effective.

Among the postoperative complications which may be encountered are: (1) Displacement of the graft, (2) infection, (3) edema, (4) delay in the formation of the anterior chamber, (5) anterior synechias, (6) iris prolapse, (7) hypotrophy, (8) hypertension, (9) keratitis, (10) hemorrhage, (11) iridocyclitis, (12) vascularization, and (13) dystrophia.

Proper coaptation of the graft is a factor of main importance in averting the first eight of these complications; it is not so significant in cases of postoperative keratitis, hemorrhage, iridocyclitis, vascularization, and dystrophia.

Complications of defective coaptation

Although it is the purpose of this paper to discuss the role of defective coaptation in producing postoperative complications, it must be remembered that causes other than the one mentioned may have played some part.

1. Displacement of the graft. This may assume three forms: (a) The graft may fall into the anterior chamber; (b) it may fall to the bottom of the conjunctival sac; or (c) ectasia of a part or the entire perimeter of the graft may occur.

Excluding cases of violent traumatism, efficient fixation of the graft will avert these mechanical accidents. Some ectasias may be the result of double mechanical errors—insufficient fixation and an oblique cut of the graft or of the trephination (fig. 1).

2. Infection. Defective closure of the anterior chamber due to faulty coaptation of the graft favors infection. When irregular cuts are made, the traumatism is greater and, therefore, the number of dead cellular elements is also greater.

Secondary infection also results from gaps in wounds, and these gaps are more easily produced if the coaptation and fixation are not perfect.

3. Edema. All authors agree on the importance of imbibition by the tears or aqueous humor in the etiology of this complication. The more perfect the coaptation of the

graft, the less frequent and intense will be the complication of edema.

4. Delay in the formation of the anterior chamber. The role of proper coaptation and fixation in this complication is quite evident. If coaptation is defective, the wound remains open at some point which allows the flux of aqueous humor. If any residue, such as Descemet's membrane, cotton fiber, and so forth, is interposed between the lips of the wound, the result is the same.

Insufficient fixation may cause intermittent gaping of the wound, with consequent intermittent loss of the anterior chamber which is evidenced by crises of tear shedding, followed sometimes by photopsias, each time the intraocular tension reaches its normal limit. Fixation in these instances is not capable of keeping the graft in place.

5. Anterior synechias. This, one of the complications most to be feared, is a consequence of delay in the formation of the anterior chamber or a traumatic gap of the wound. Many opacifications of the graft and a large number of postoperative glaucomas are due to anterior synechias. A good cut and fixation constitute the most effective prophylaxis.

6. Iris prolapse. This complication, which has the same etiology as those previously mentioned, fortunately is quite uncommon for its consequences are serious.

7. Hypotrophy. The French-Swiss school classifies the opacifications of the graft into two large groups: 1. Opacifications of evident origin. 2. Opacifications with no evident cause or illness of the graft.

Personally, and because of considering the term as more didactic and especially more suitable to the needs of the clinic, I have preferred to give the name of hypotrophy to the group of opacifications included in the term illness of the graft. This term also indicates the pathogenesis of the alteration in transparency.

The loss of transparency through hypotrophy starts approximately 20 days after operation or later. Only as an exception does it occur earlier because for about three weeks, the graft maintains its transparency at its own expense.

It is during this period of transition, when the metabolism of the graft becomes entirely dependent upon the bed and when the nutrition is insufficient, that a more or less intense hypotrophy may appear more or less rapidly.

Generally, this complication begins with a diffused turbidity that is a little more accentuated in the center of the graft which is edematous. Slitlamp examination shows an enlarged cornea that may attain a thickness two or three times greater than normal, or even more, especially in the center. The epithelium shows some vesicles and has an unglazed appearance; it is missing at certain points which stain well with fluorescein.

Besides the edema, the tissue itself shows more intense foci of opacification which are irregularly distributed and which are located on different planes. Generally, the periphery is more transparent. On the other hand, it is not exceptional to find a perfectly transparent zone of from 0.5 to 1.0 mm. in the entire circumference.

Descemet's membrane shows folds in various directions. These folds frequently constitute the first indication that there is a deficiency in nutrition and that the host is not in a condition to maintain the normal metabolism of the graft.

The graft may not receive a sufficient quantity of the elements necessary for its metabolism because of: (1) The nature of the corneal disease, (2) profound uveal disturbance, (3) disturbance of the precorneal lacrimal film, (4) thinness of the receiving cornea or excessive thickness of the graft in nonpenetrating keratoplasty; (5) faulty coaptation of the border of the wound, or frequent gaping, which determines a secondary cicatrization with neoformation of conjunctival tissue, improper for the biologic interchange; (6) displacement of the graft.

I have explained in other reports the clinical and anatomicopathologic basis of this conception. However, considering exclusively the complications produced or favored by a defect of coaptation or fixation of the graft, it will be seen that the last three causes of hypotrophy are exclusively due to it.

In penetrating keratoplasty, it is essential to place the graft in a cornea of normal thickness or one which has previously been made normal. In nonpenetrating keratoplasty, the hypotrophy is more uncommon. I have seen it only in cases of an exceedingly thick graft and, even in such case, the hypotrophy is limited to the zone of maximum protrusion. In these cases the symptoms are characteristic but their appearance is much more tardy.

In partial displacements of the grafts symptoms of hypotrophy may appear in the ectatic zone.

8. Hypertension. This complication may be due to faulty coaptation or insufficient fixation. A delay in the formation of the anterior chamber may favor the appearance of an iridocyclitis with hypersecretion, which will produce hypertension as soon as the fistula has healed.

It is not necessary to point to the importance of anterior synechias in causing hypertension, and their relation to coaptation and fixation has already been mentioned.

After experience with a number of the surgical techniques employed in penetrating keratoplasty and careful study of the postoperative progress of each, comparing their results, I have reached the conclusion that most of the postoperative complications which cause a delay in the normal healing process or even the failure of the operation are directly imputable to defective coaptation of the graft.

By using the technique about to be described, I have obtained most satisfactory results and have had almost no postoperative complications.

Description of technique

It must be borne in mind that:

1. Penetrating keratoplasty for sight restoration must be performed as an exclusive surgical act during which no manipulations other than those strictly necessary for replacing the pathologic cornea with the graft ought to be undertaken.

2. The operation must be carried out in an eye absolutely free from any active inflammation, with a cornea of normal thickness in the region which borders the graft, and with a normal or normalized anterior chamber and ocular tension.

3. Any intervention necessary to establish the aforementioned preoperative conditions (nonpenetrating keratoplasty, synechiotomy, cyclodialysis, iridectomy, and so forth) has to be executed beforehand; no graft should be implanted while there is still the least reaction.

Size of graft

Prior to any transplantation procedure, the most suitable size for the graft should be determined. Small grafts (4 mm. or less) are of little use and show a tendency to invasion by the host. Large grafts (over 6.5 mm.) may create postoperative disturbances. Grafts varying in size between 5.0 mm. and 6.5 mm. are to be preferred, but the most suitable size has to be determined for each individual case, keeping in mind:

1. The graft must be absolutely centered with the pupil.

2. The graft has to border on cornea of normal thickness.

Respecting these principles, our preference is for trephinations of from 5.0 to 5.5 mm. and in most cases, these will suffice. If, however, 5.0 to 5.5-mm. trephinations do not extirpate the greatest part of the pathologic cornea, trephines of 6.0 or 6.5 mm. may be used, but it would be imprudent to use still larger sizes. If the nature of the lesions makes failure to be feared, the wise procedure is to improve the ground by per-

forming a nonpenetrating keratoplasty.

Much attention has to be paid to the thickness of host cornea bordering on the graft, for this, too, determines the diameter of the trephination. A graft on a thicker or thinner cornea will most probably fail. Generally speaking, this condition prevails in those cases in which sight is still present before operation. Corneas are usually thinner in the center, and it is necessary to perform the section in a cornea of normal thickness. When trephinations of the preferred dimensions cannot be attained, a previous nonpenetrating keratoplasty becomes necessary to normalize the thickness and secure good nutrition for the graft. If the cornea is very thick (total leukomas), a superficial keratoplasty has to be performed to thin out and, at the same time, improve the bed. Such a procedure is superior to a keratectomy because healing is more rapid and the results are better (fig. 2).

Usually, we make use of round grafts of a size similar to that of the resection; only in myopic eyes or in eyes with corneal ectasia is it preferable to use a graft smaller by 0.1 mm. in order to reduce the corneal curvature and at the same time improve the ametropia.

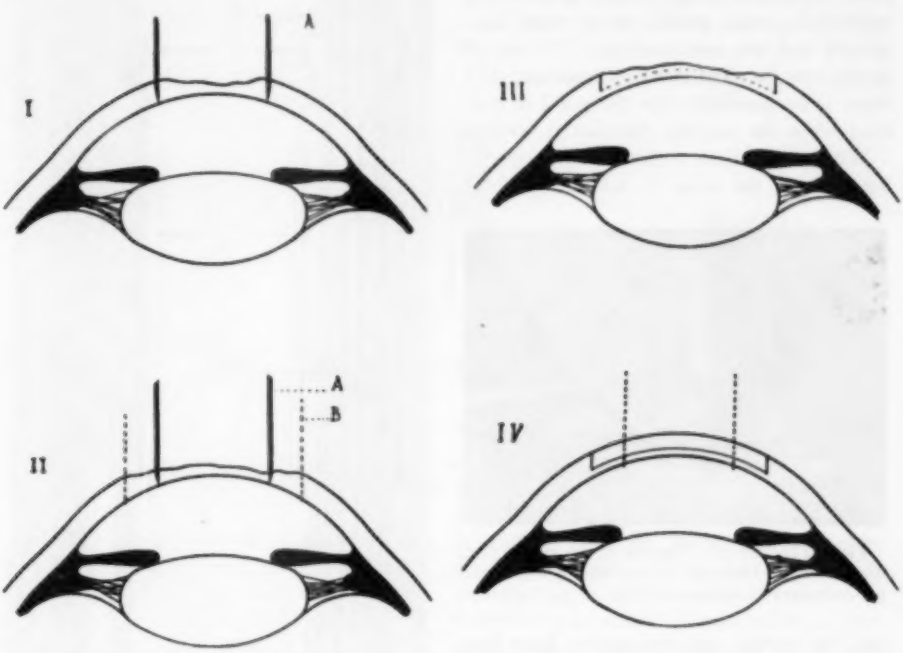

Fig. 2 (Barraquer). (I) A 6.0-mm. trephination allows one to make a section in cornea of normal thickness (correct). (II) A 6.0-mm. trephination (A) would lead to a section in thinned-out cornea (wrong). An 8.0-mm. trephination would effect it in normal thickness (B), but that size is dangerous in penetrating keratoplasty. (III) Shows the dimensions of a nonpenetrating keratoplasty to be performed in an instance such as shown in (II). (IV) The cornea having attained its normal thickness, a penetrating operation of adequate size can be carried out in all security.

Operating procedure

Operating while the pupil is kept in miosis with eserine has the follow advantages: (1) Permits more perfect centering of the

graft with the pupil; (2) greater cleanness of trephination because of better visibility of the chamber depth; (3) better protection of the lens and better visibility, if the trephination must be completed with a different instrument; (4) less danger of anterior synechias being formed, particularly sphincteric ones which occur most frequently and are most noxious; (5) not all pupils can be dilated to the utmost; (6) there is no possibility for the pupil to contract when the anterior chamber is opened.

When the patient comes into the operating theater, the pupil is miotic (eserine)

Fig. 3 (Barraquer). Fixation of the eyeball with the Barraquer-Lloveras forceps during the trephination to prevent it from rotating.

and the cornea and conjunctiva have been anesthetized by instillation of a four-percent cocaine collyrium with adrenalin every five minutes until the moment when trephination begins.

The operating sequence is: (1) akinesia of the orbicularis; (2) retrobulbar injection; (3) trephination; (4) obtaining the graft; (5) placing the graft; (6) suturing.

1. Akinesia of the obicularis. This may be brought about by means of any preferred technique (Van Lint, Villard, Barraquer, O'Brien, and so forth).

In the first two techniques, if the orbicularis does not respond promptly, a few drops of alcohol may be added to attain a concentration of 10 to 30 percent, according to each case, as well as to secure a greater postoperative quietude and better docility during the first dressings. As soon as akinesia is perfect, retrobulbar injection is performed.

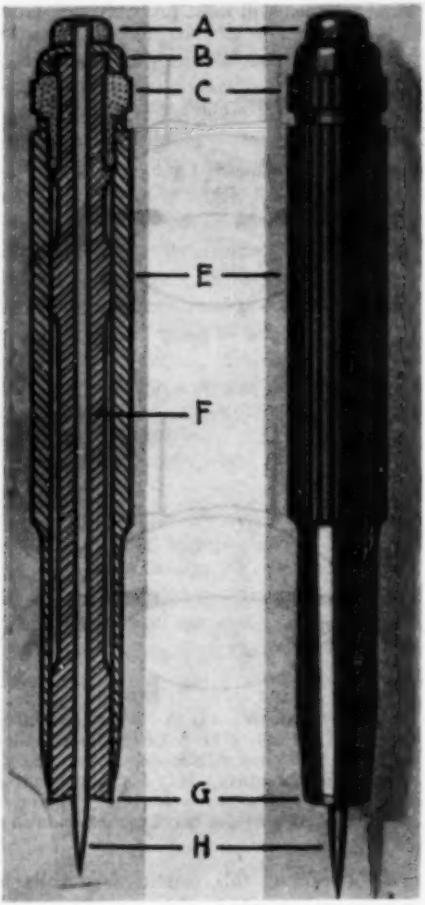

Fig. 4 (Barraquer). Trephine (Barraquer) for penetrating keratoplasty and lamellar grafts. (A-H) Central punch. (C) Micrometric screw. (G) Internal butt, for limiting the depth of section in lamellar plasties and to protect the edge when the instrument is not in use.

2. Retrobulbar injection consists of one cc. of novocain (two percent) with 0.0001 suprarenine and 10-percent alcohol for sup-

pressing during the first days all axial reflexes starting from the cornea.

Stitches placed in the cornea act as foreign bodies and provoke pain and ciliary reactions. Very often the patient is obliged to move his eyes and to contract the orbicularis, thus causing gaps in the wound with corresponding delay in healing, as well as a flux of aqueous humor from the wound and danger of anterior synechias being formed.

Franceschetti centrator in the shape of a horseshoe may be used, or else a ring with a handle, or, better still, a trephine similar to Paufique's or the one I have invented (fig. 4) following like principles. It is provided with a central pin (fig. 4-H) to be placed upon the cornea centered with the pupil, and the trephine glides over it (fig. 5).

The advantage of this trephine is that all

Fig. 5 (Barraquer). The trephination is strictly centered with the pupil, the trephine gliding over the punch, which has previously been centered with the pupil.

Objective manifestations of such iridociliary reactions are slight palpebral edema, blepharospasm (photophobia), slight perikeratic hyperemia, and difficulty in dilating the pupil.

In many cases, a retrobulbar injection containing 10-percent alcohol totally suppresses such troubles. No higher concentration can be recommended for surgical treatment because of the orbital edema which may accompany it.

3. Trephination. While the eyelids are being held back by a lid retractor the trephination should be effected two minutes after the retrobulbar injection. A longer delay would oblige operation on a hypotonic eye, thus endangering the uniformity of the section.

During the trephination, the eyeball should be immobilized with Barraquer-Lloveras forceps which entirely prevents it from rotating (fig. 3). For centering it, a

operations may be performed with one single instrument, without any necessity of withdrawing it after starting the section. It is useful in penetrating keratoplasty, as well as in laminar interventions, for which purpose it is provided with a special butt (fig. 4-G).

If a good section is to be obtained, the

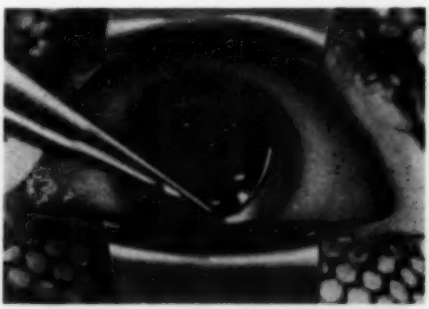

Fig. 6 (Barraquer). The section is completed with scissors without stretching the cornea.

Fig. 7 (Barraquer). Vessel (Barraquer) for preserving eyeballs in moist chamber.

position of the trephine has to be absolutely vertical; its rotating movements must be as ample as possible, while pressure is softly and uniformly brought to bear upon it (fig. 5).

Use of a four-mm. trephine effects a full trephination in nearly every case, without any risk to the lens. If a somewhat larger trephine is used, frequently the section will be incomplete and will have to be finished with some other instrument. A small knife may be used when the hinge is small; a pair of scissors when it is larger. After trying out several models of curved scissors especially made for this purpose, I prefer Castroviejo's scissors or, in the absence of them, the Barraquer pincer-scissors which, althought straight, are very easy to handle (fig. 6).

In no case must the cornea be stretched to complete the section. This would produce an irregular section of Descemet's membrane which is very elastic.

As soon as the trephine is withdrawn, the graft should be prepared. Doing this will allow time for the retrobulbar injection to increase the hypotony of the eye. Although it is not convenient to section a hypotonic eye with the trephine, hypotonicity represents a safety factor for the rest of the procedure, especially if the section has to be finished with the scissors.

4. Obtaining the graft. We prefer adult cornea taken immediately after death and

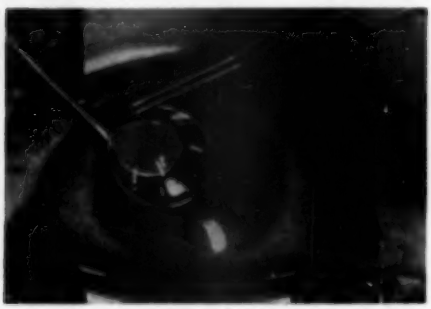

Fig. 8 (Barraquer). Placing the graft.

Fig. 9 (Barraquer). Greatly enlarged point of the needle (Barraquer) for corneal suture. The photograph shows only the anterior third of the needle, its total length being six mm. and its radius of curvature, five mm.

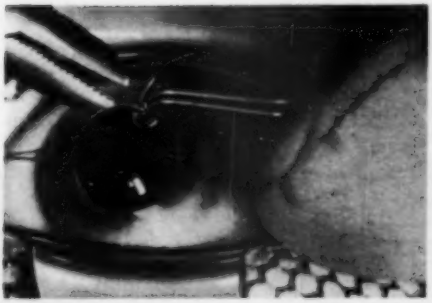

Fig. 10 (Barraquer). Placement of the first stitch of suture.

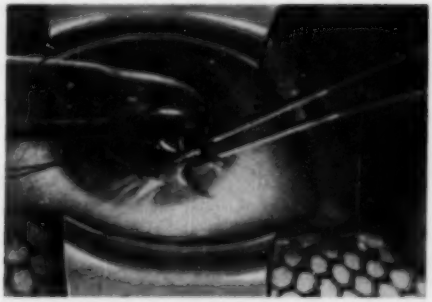

Fig. 11 (Barraquer). Placement of the last stitch of suture.

preserved for 12 to 36 hours in the ice-box, in moist air, at a temperature of 2°C. to 4°C. (fig. 7). Preservation at that temperature brings about a loss of individuality in the tissue, making the graft more easily tolerated. The graft has to be entirely carved out with the trephine and should be rejected if there is even the slightest irregularity. The graft is washed with physiologic saline solution and handled by means of a Franceschetti spatula.

5. *Placing the graft.* With the forceps, the desiccated disc of the pathologic cornea is withdrawn (it has been left in the trephination as an operculum), and the new cornea is carefully positioned (fig. 8).

6. *Suturing.* Suturing the graft is the most important step in the operation for the success of the procedure depends almost entirely upon it. As has been discussed, most postoperative troubles are due to faulty or incorrect fixation.

Direct suturing of the graft with fine silk thread and extremely sharp five-mm. needles (fig. 9) (Grieshaber) with downward cutting edge (Barraquer) guarantees the best results.

The graft, positioned in the recipient's

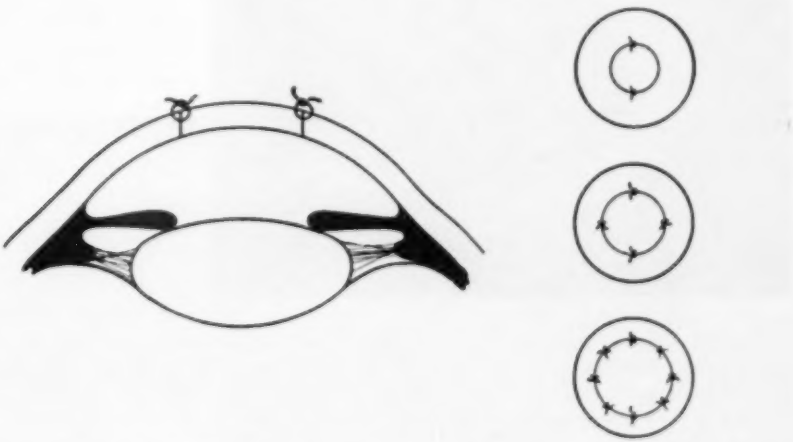

Fig. 12 (Barraquer). The stitches must go through one half the thickness of the corneal parenchyma, and should be placed in a larger or smaller number according to the diameter of the transplantation and conditions of each case (at right).

trephination, is fixed by means of a Hess forceps so placed that only the anterior layers of the graft are taken up between the prongs. The suturing needle enters through the epithelial face of the graft, quite near the fixing point of the forceps, and goes out through the center of its thickness; it penetrates, exactly in front, into the surface of the host's section (figs. 10 and 11).

In the 5.0-mm. grafts, it is sufficient to suture two points at the extremities of the 6- to 12-o'clock meridian. Grafts of 6.0 mm. need at least four stitches, if not more.

Great care must be taken so that the points where the needle comes out of the graft and where it enters the host are situated exactly upon the same radius. If this is not done, the resulting deformity in the graft would contribute to defective coaptation and fistula of the anterior chamber, with all the troubles which we are striving to avoid (fig. 12).

The operation ends with careful irriga-

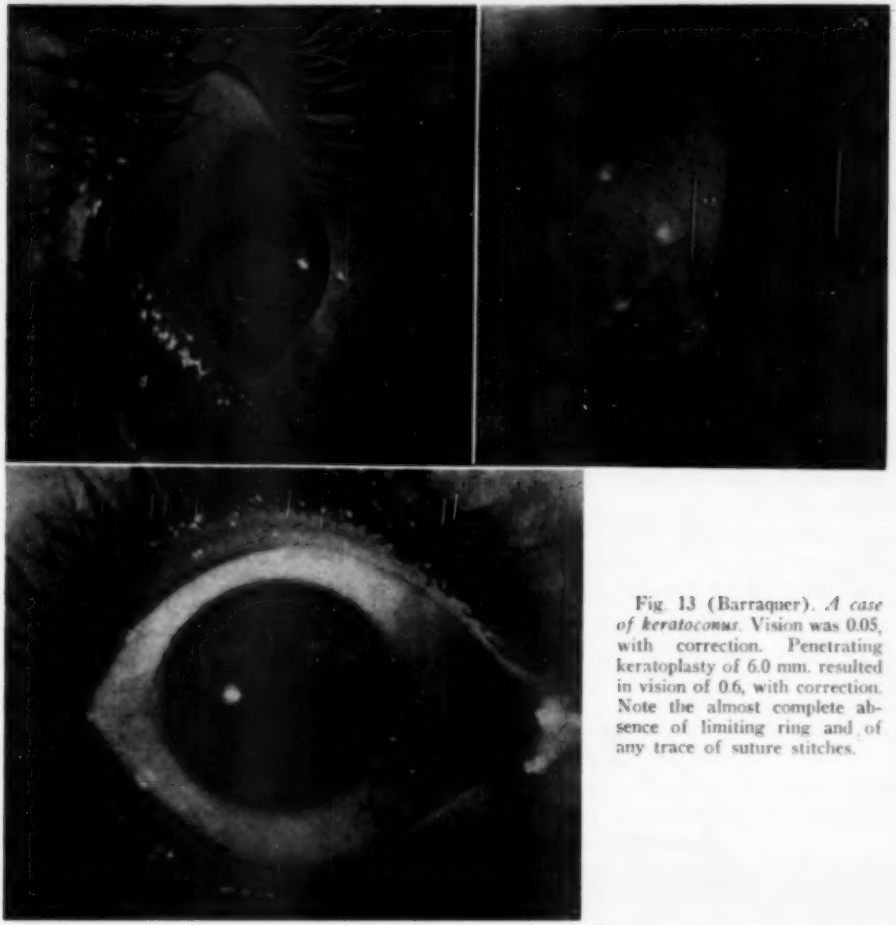

Fig. 13 (Barraquer). *A case of keratoconus.* Vision was 0.05, with correction. Penetrating keratoplasty of 6.0 mm. resulted in vision of 0.6, with correction. Note the almost complete absence of limiting ring and of any trace of suture stitches.

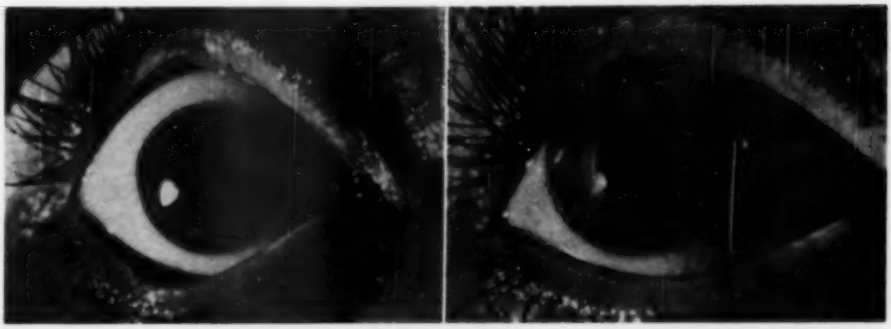

Fig. 14 (Barraquer). *Leukoma caused by rosaceous keratitis.* Vision was 0.03. Penetrating keratoplasty of 5.0 mm. Postoperative vision was 0.3.

tion of the bottom of the conjunctival sac with saline solution and instillation of an eserine collyrium and a few drops of penicillin solution. A binocular dressing is applied, with a protecting mask of fiber or cardboard as after cataract extractions. The patient must stay in bed for 12 days but, if the bed is a mechanical one, he may sit up whenever he likes.

At the first dressing on the third or fourth day, an atropine collyrium (2.5 percent) is instilled. Further dressings are done every two or three days. On the fourth day, if indicated, a saline aperient or mild laxative may be prescribed.

After 10 days, a monocular dressing is applied, and the patient may get up. The sutures are withdrawn in about 14 days. The dressing may be removed after 17 days in 5.0-mm. trephinations; after 20 days in 6.0-mm. trephinations; and after 22 days in trephinations of 6.5 mm.

Mydriasis (never miosis) must be maintained when the slightest reaction (hyperemia or photophobia) is present. In cases of increased ocular tension, a cyclodialysis or an Elliot trephining operation may be performed. In such cases, mydriasis should be continued.

Conclusion

This technique, incomparably safer and more certain as to outcome than all other keratoplasty techniques employed at pres-

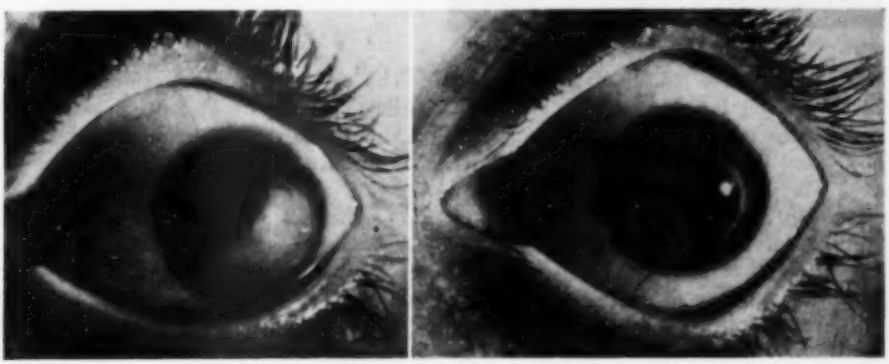

Fig. 15 (Barraquer). *Leukoma caused by phlyctenular keratitis.* Vision was 0.2. Penetrating keratoplasty of 6.0 mm. Postoperative vision was 0.7.

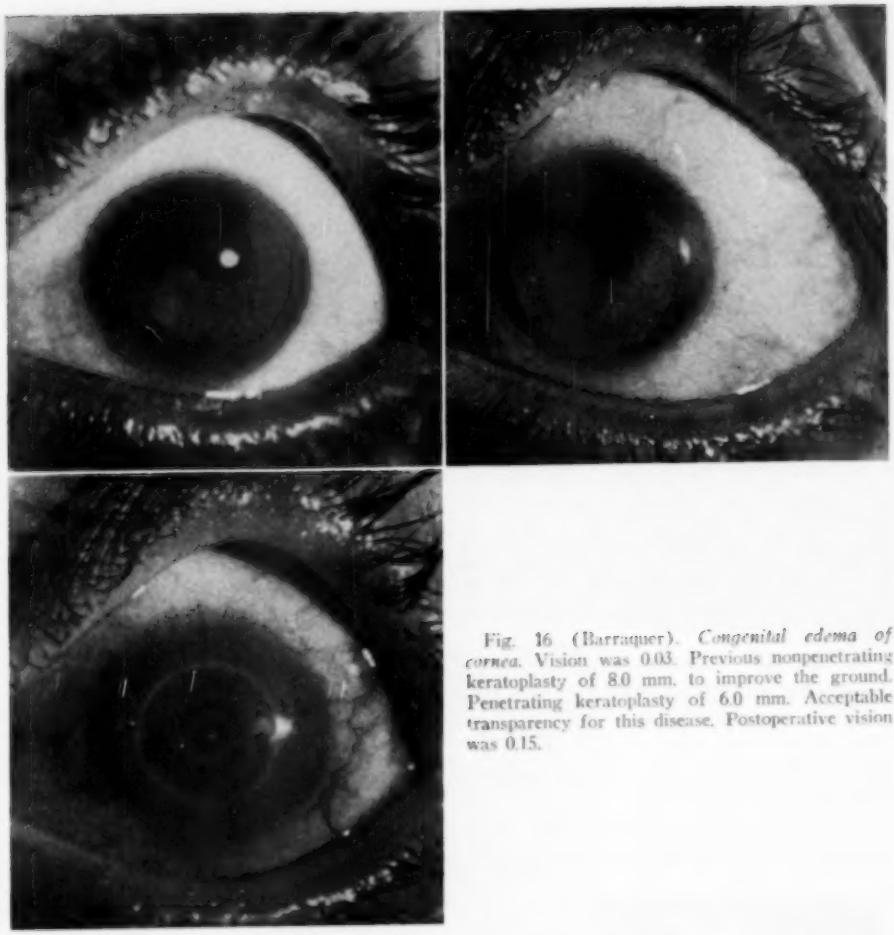

Fig. 16 (Barraquer). *Congenital edema of cornea.* Vision was 0.03. Previous nonpenetrating keratoplasty of 8.0 mm. to improve the ground. Penetrating keratoplasty of 6.0 mm. Acceptable transparency for this disease. Postoperative vision was 0.15.

ent, is much more difficult to carry out as far as suturing is concerned. It is absolutely essential to operate in a dark room with good focal lighting limited to the operating field. The operator should be seated behind the patient's head, with his forearms supported, and he should wear a binocular loupe. If any of these conditions are lacking, or if the suturing needles are not extremely sharp, it is better to place a bridging suture, even though the results will be less certain.

The excellent results obtained with this technique are shown by the high percentage of definite transparencies, by the absence of postoperative complications, and by the absence of a limiting ring. As far as I can judge, the presence of a limiting ring means simply a secondary cicatrization. It is not, however, the defense of the graft against its pathologic surroundings (figs. 13 to 16).

By using this technique of penetrating keratoplasty, it is possible to make a more certain and favorable prognosis.

Discussion

Dr. H. M. Katzin (New York): Dr. Barraquer has shown a very nice technique and has emphasized several points that we would all do well to note. The importance of coaptation of the wound margins cannot be overemphasized. The use of the specially made needles and trephines is a considerable help in obtaining good surgical results.

The use of alcohol for prolonged retrobulbar anesthesia is not a common practice in this country and certainly would be worth trying. We agree with Dr. Barraquer that adult corneas preserved at ice-box temperature for not more than three days is the best method we know of so far for preserving the graft. We have not used the direct suture as a routine method in keratoplasty except when very large grafts are used. The postoperative instillation of eserine is also something we have not employed, but Dr. Barraquer presents some convincing reasons for miosis.

THE COMPLICATIONS OF PENETRATING KERATOPLASTY

Their prevention and treatment

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In penetrating keratoplasty, the complications are very different in the easiest cases—Groups 1 and 2 of the American classification—and in the cases of Groups 3 and 4, which we may call complicated cases.

In the first two groups, the greater number of complications arise from technical mistakes. In Groups 3 and 4, the original lesions of the eyeball are generally responsible for these complications.

I. Easiest cases

A. Technical errors during the operation

1. Mistake in placing the graft is very frequent and has the greatest importance concerning the final vision. Although it is sometimes possible to correct it by a contact glass, it very often makes a second keratoplasty necessary. It is avoidable only by good technique.

a. When a mobile pupil permits it, the center should be marked during the miosis to make possible the use of Paufique's marking trephine during the operation.

b. If posterior synechias or previous iridectomy makes this too difficult, such rings as Lohlein's or de Saint-Martin's may be used during the operation.

Fortunately, sufficient training usually makes it possible to avoid this mistake, but it is very important always to be very careful in placing the graft.

2. Oblique resection of the cornea. This may cause displacement of the graft; and, in any event, it leaves too large and very unpleasant scars.

In order to avoid this, it is of great importance to obtain good fixation of the eyeball. After good akinesia of the four recti, stitches are placed in the internal and external recti and are held firmly by an assistant. With his left hand, the surgeon, himself, holds the conjunctivo-episcleral tissue with forceps placed a short distance from the limbus. Both the surgeon and the assistant should make certain that the direction of the trephine incision is exactly correct.

It is much easier to obtain a good section of the graft itself. However, it seems important to place the donor eye flat on the table instead of having it in the hand. It is

also necessary, in order to avoid a crest graft, to exert a sufficient, but not too great, pressure with the fingers.

3. Deficient cutting. A mistake of great importance in determining the final results is the deficient cutting of the deepest layers of the cornea, especially of the Descemet's membrane. This cutting must be perfect for the graft as well as for the recipient eye.

If a good section is to be made on the donor eye, a sharp trephine must be used. The instrument should be pushed quickly into the lens. The graft should be carefully washed in a penicillin solution to rid it of any particle of iris tissue.

The resection of the host is more difficult because of the irregular thickness of the cornea and the risk of hurting the iris or the lens.

In my own experience, the cutting of Descemet's membrane should always be done with scissors, especially in cases with flat anterior chambers. Sectioning with the trephine must be stopped as soon as the anterior chamber is opened, the part of the cornea to be resected being firmly held with forceps on the border (and not with a stitch in the center). The scissors should be introduced under the cornea to get a membrane flap slightly larger than the section of the anterior layers.

A poor section of Descemet's membrane hinders correct placing of the graft and very often produces a dangerous proliferation of the membrane on the posterior surface. The rest of the membrane must be carefully cut out, either with scissors and forceps or with a special punch constructed for that purpose.

4. Misplacing the corneal stitches. Whatever kind of suture is used—continuous or discontinuous—(I generally prefer the latter)—they may be too superficial or penetrate too far into the anterior chamber. Superficial stitches are not secure enough to keep the graft in the right place for a sufficient period. Penetrating stitches may complicate the operation. In such an event, it is necessary to be very careful in the opening of the flat anterior chamber. If perforating sutures are overlooked, a delay in the reforming of the anterior chamber will always occur, with very dangerous adherences between graft and iris.

Such technical mistakes can be prevented or easily corrected. It is not always the same with postoperative complications.

B. Postoperative complications

Some complications are the consequence of technical errors but, even in the easiest cases, a great many complications cannot be prevented, such as the insubordination of noncoöperative patients.

The most frequent among the many complications which are observed after a penetrating keratoplasty are: (1) displacement of the graft, (2) deformity of the graft, (3) the adhesions between the graft and iris, and (4) secondary glaucoma.

1. Displacement of the graft is very often the consequence of an oblique resection, of remains of Descemet's membrane, or of insufficient sutures. Even with correct technique, there is always a possibility of this complication in noncoöperative, nervous, too old, or too young patients. Nystagmus can also be responsible. Here translid muscular sutures or alcoholization of the recti muscles may be of help.

In an early displacement, correction may be possible. If it has remained clear, the graft may be put back in the right place and firmly held with edge to edge stitches. In some such cases, it has been possible for me to obtain very good results. Sometimes new grafts, generally a little smaller than the first one, have to be used. It is always dangerous to leave the hole wide open. The use of a conjunctival flap seems to me to be really unsuccessful for a functional recovery.

2. A deformity or abnormal thickness of the graft, although frequent, but less dangerous, will give very marked astigmatism with poor vision. It has been especially ob-

served when using grafts coming from too young donors, children and babies. I think the best donors are old people.

This complication seems to be produced more often by retraction of the recipient cornea. After using for a long time the same size trephines to remove the grafts and to make their bed in the recipient cornea, I prefer nowadays to use different trephines —5.0 and 5.1 mm. and 6.0 and 6.1 mm.— the larger being reserved for the corneal resection.

Trephines with greater differences in size may be used. For keratoconus, 2 or 3 tenths of a millimeter, sometimes more, are useful because of the pathologic thinness of the tissue. In such cases the square transplantation, which permits one to modify the size of the graft, is preferable.

In treating conical deformities and modifications in a graft's thickness, I prefer the technique of Dr. Fritz who, at the end of the operation, places a contact glass of determined curve directly upon the graft so that correct pressure is applied *ipso facto*.

Much has been said about the refusal of the recipient eye to accept the graft but I have never observed this complication. Since prevention is impossible, the only treatment would be a second keratoplasty.

3. Adhesions between graft and the iris are the most frequent and, in my experience, the most dangerous of all complications of penetrating keratoplasty.

A widely dilated pupil is certainly of major importance in avoiding this complication. For that purpose, the use of atropine drops is not sufficient and dilatation should be increased by instillation, or subconjunctival injection, of a concentrated solution of adrenalin (two percent). This can be repeated at the end of the operation.

In some cases with previous iridectomy or posterior synechia, especially when large grafts (6.0 or 7.0 mm.) are used, the sphincteric part of the iris remains opposite the place of trephination. When this occurs, miotic ointments (eserine, D.F.P.) can be used. I think it is less dangerous to leave the flat part of the iris behind the graft rather than the sphincter itself.

Every time the iris is touched, adhesions may be produced. Adhesions may also result from hemorrhages from corneal vessels. Bleeding has to be carefully stopped. Every delay in reforming the anterior chamber is also dangerous.

Any adhesion must be destroyed as quickly as possible. Sometimes mydriatic drops or ointments at the time of the first dressing may be sufficient. Generally an operation becomes necessary. A very small synechia may be treated by a simple iridectomy. For wide synechia, Castroviejo's cyclodialysis technique must be used. In all such cases, operation should be performed at the end of the second week. Sometimes trauma causes the anterior chamber to reopen after the patient leaves the hospital and produces a late synechia, which can often be observed only after many weeks. In such cases, the circular or square incision, described by Paufique, is the only way in which the entire synechia can be destroyed.

It must be emphasized that every adhesion between the iris and the border of the graft disturbs the graft—and must be loosened.

4. Secondary glaucoma seems more infrequent after a penetrating than after a lamellar keratoplasty. In my opinion, it is generally an inflammation, really an iridic glaucoma. We can observe it especially in cases with severe alterations of the iris.

The best means of prevention is certainly a previous iridectomy, about which we have often spoken.

The treatment must be surgical—iridencleisis or sclerecto-iridectomy (Elliot's technique) with total iridectomy. If frequent anterior synechias have to be destroyed, cyclodialysis is indicated. It is sometimes possible to get valuable results with flat cyclodiathermy.

Preventive or special surgical treatment

cannot avoid the "malady of the graft"—late opacification without evident reason—which Offret thinks is the result of the destruction of donor keratoblasts. When not self-curable, one is obliged to perform a second keratoplasty that sometimes may be only lamellar and made in the neighborhood of the first penetrating graft. The first results obtained with subconjunctival corneal implantation were unsatisfactory. Very often a second penetrating keratoplasty had to be done.

2. Complicated cases

The prognosis of penetrating keratoplasty is very different indeed in complicated cases—very extensive vascularized leukomas, anterior synechias, conjunctival or palpebral alterations.

The general rule is to do preliminary operations in order to prepare for keratoplasty

A. Very extensive leukomas

The extent of the leukoma is, in my opinion, not the most important factor in determining success. I do not think that the cases "where the transplant will be surrounded in more than one half of its circumference by dense scar tissue" (Castroviejo) are always unfavorable cases. The thickness of the leukoma is, to me, more important than its extent. I have obtained very satisfactory and lasting results in post-ulcerous leukomas, where the graft was placed in the middle of dense scar tissue. It is, however, true that total leukomas do not generally give good results. In these cases, a previous total lamellar keratoplasty should be done. In favorable cases, this will soon provide very marked improvement of the scar.

B. Extensive vascularization

This can really produce complications of the greatest importance.

In the case with a superficial layer of vessels, the best measure of prevention seems to be not the keratectomy, but a total lamellar keratoplasty. Often new vessels will penetrate the graft, but they will generally be less important.

In cases with interstitial vascularization, the lamellar graft is, on the contrary, of very little value. During the operation we have to wait for the end of the hemorrhages. The anterior chamber must be carefully cleaned of any blood clot. In such cases, the results are very often good.

However, a few days after the operation, some new vessels may sometimes be seen in the graft. Careful examination is, therefore, very important so that X-ray treatment can be given as soon as possible. The earlier X-ray treatment is started the better will be the results. The usual treatment consists in 50 r. A total of 200 r to 250 r may be sufficient to stop vascular invasion of the graft.

C. Anterior synechias

Attempts to eliminate anterior synechias must generally be made before the corneal transplant operation.

In some cases, however, it has been possible to obtain clear grafts without previous treatment of the synechias. A very good result has persisted in such a case operated by Dr. Castroviejo last year during the meeting on keratoplasty in Nantes.

Generally the anterior synechias are very important in the production of glaucoma or of adhesions of the iris to the graft, with very bad visual results.

The prevention of such accidents requires considerable effort. One of the best methods is certainly that recently described by Paufique: circular or square incision around the leukoma with a knife or a trephine. This method suffers the same complications as the usual methods, but obtains more complete results.

D. Symblepharon; Lid defects

These conditions must be carefully treated before keratoplasty and much time

must often elapse between treatment of the eyelids and the keratoplasty.

Conclusion

Progress in the treatment of corneal scars has been very definite in the last five years. Before that time, complications in keratoplasty did not seem to be due to technical mistakes, even in the easiest cases. Perhaps such improvements have been made possible only by communication which, fortunately, is now easier between the great number of surgeons working on corneal transplantation.

May all the subjects be as universally studied as keratoplasty, and may on the border of our common sea exist the friendship possibilities which have already permitted us the "union of the graftists!"

STATISTICS ON RESULTS OF KERATOPLASTY

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In the Manhattan Eye, Ear, and Throat Hospital at the present time, we are making a statistical study of keratoplasty. In order to eliminate the varying factor of surgical technique, only grafting operations done by one surgeon—Dr. R. Townley Paton—and only those operations done with the same or quite similar technique are considered in this report.

The plan of this study has been to list consecutively, according to the date of the operation, the cases on large graph sheets. The data from the histories and operative sheets have been summarized and the pertinent data have been written under the patient's name. From the files of the Eye-Bank laboratory complete data on the donor eyes have been obtained and added to the graph sheets.

Only those cases that have been followed for four months or longer have been considered in this study. Any cases with inadequate follow-up information have been eliminated.

For purposes of standardization and accurate comparison, the material thus obtained has been analyzed according to the criteria as set up by Owens and others[1] under the sponsorship of the American Academy of Ophthalmology and Otolaryngology.

This report deals in part with the final results in 100 cases of partial penetrating keratoplasty. Only the clarity of the transplanted corneal tissue will be discussed at this time. The correlation of the final visual acuity and refractive errors, as well as the study of donor material as it affects the final results, will be published elsewhere.

In the group as a whole, 55 percent of the grafts remained clear and 45 percent became cloudy. Thus without selection of cases, there was better than one chance in two that the graft would remain clear.

Table 1 indicates the relationship between the patient's age and the final clarity of the graft. The youngest patient in our series was aged 17 years; the oldest, 70 years. In the 21- to 30-year age group, there were 18 clear grafts; only two were cloudy. However, the great majority of patients in this age group

TABLE 1

Relationship of Age of Patient to Final Result

Age Group	Clear	Cloudy	Total
10–20	2	3	5
21–30	18	2	20
31–40	7	10	17
41–50	12	13	25
51–60	9	12	21
61–70	5	6	11

TABLE 2

RELATIONSHIP OF DIAGNOSIS TO PERCENTAGE OF CLEAR GRAFTS

Diagnosis	No. of Cases	Clear Grafts (followed four months or longer)
Conical cornea	20	85%
Hereditary dystrophy	8	100%
Scar luetic interstitial keratitis	12	50%
Scar T.B. interstitial keratitis	3	0
Scar nonspecific inflammatory	42	42.8%
Scar chemical	6	0
Scar traumatic	8	50%
Scar trachomatous	3	2 clear
Fuch's dystrophy	3	0
Mooren's ulcer	1	0

were those with conical cornea. Therefore, there is no real relationship between the age of the patient and the final result.

Table 2 deals with the relationship between diagnosis and the percentage of clear graft. In eight cases of hereditary dystrophy, all grafts have remained clear. In 20 cases of conical cornea, 85 percent of the grafts have remained clear. In the largest group (those cases classified as scars due to nonspecific inflammatory conditions) 42.8 percent of the grafts have remained clear. In two out of the three cases of scarring due to trachoma, the grafts remained clear. No improvement was seen in any cases of Fuchs's dystrophy, chemical burn, or tuberculous interstitial keratitis.

In Table 3, the preoperative size of the corneal opacity has been correlated with the final clarity of the graft. In those cases in which only central opacities were present, 74.3 percent of the grafts remained clear. Close behind this group were those cases with opacities involving less than one half of the cornea with a final clarity of the grafts in 67 percent. When opacities involved over one half of the cornea, only 36 percent of the grafts remained clear.

TABLE 3

RELATIONSHIP OF SIZE OF CORNEAL OPACITY TO PERCENTAGE OF CLEAR GRAFTS

Size of Opacity	No. of Cases	Clear Grafts (followed four months or longer)
None	1	0
Central	35	74.3%
One half or less	6	67%
Over one half	9	36%

Table 4 shows the relationship between preoperative corneal vascularization and the percentage of clear grafts. Cases with no vascularization had by far the best percentage of clear grafts; namely, 71.7 percent.

TABLE 4

RELATIONSHIP OF CORNEAL VASCULARIZATION TO PERCENTAGE OF CLEAR GRAFTS

Vascularization of Cornea	No. of Cases	Clear Grafts (followed four months or longer)
None	53	71.7%
Slight	22	45.5%
Moderate	22	22.7%
Extensive	2	0

TABLE 5

RELATIONSHIP OF PROGNOSIS TO PERCENTAGE OF CLEAR GRAFTS

Prognosis	No. of Cases	Clear Grafts (followed four months or longer)
Very good	23	82.7%
Less good	36	69.4%
Unfavorable	32	31.3%
Contraindicated	11	9.1%

With slight vascularization, 45.5 percent of the grafts remained clear; and with moderate vascularization, only 22.7 percent remained clear. In two cases with extensive vessel in-growth, neither graft remained clear.

Table 5 shows the relationship between prognosis and percentage of clear grafts. The cases in this selection have been grouped according to the criteria for prognosis described by Castroviejo.[2] Group 1

contains those cases with a very good prognosis and includes patients with mild keratoconus, slight central scarring, and mild interstitial keratitis. Out of the 23 cases in this group, 82.7 percent showed clear grafts.

In Group 2 are the cases in which the prognosis was not so favorable—hereditary dystrophy, extensive superficial corneal opacities without vascularization, adherent leukoma, central descemetocele, and extensive interstitial keratitis. Of the 36 cases in this group, 69.4 percent had clear grafts.

Group 3, unfavorable for keratoplasty, includes cases of corneal scarring involving the limbic and pupillary portions of the cornea, extensive deep leukomas, band-shaped degenerations, and opacities with vascularized pannus. Of the 32 cases in this group a surprising number (31.3 percent) showed clear grafts.

Group 4 includes cases in which keratoplasty is contraindicated, such as Fuchs's dystrophy, extensive opacification, calcareous degeneration, and eyes with massive anterior synechias. Of the 11 cases in this group, only 9 percent resulted in clear grafts.

Summary

One hundred cases in which partial penetrating keratoplasty was done by Dr. R. Townley Paton have been presented. Without selection, in 55 percent of these cases the result was clear grafts; 45 percent ended with cloudy grafts.

When there is proper selection of cases, a high percentage of clear grafts can be obtained.

Cases most suitable for keratoplasty are those of conical cornea, small central opacities, and mild interstitial keratitis. The larger the opacity, and the more extensive the preoperative corneal vascularization, the less chance there is for a final clear graft.

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2. Castroviejo, R.: Indications and contraindications for keratoplasty and keratectomies. Am. J. Ophth., 29:1081-1093, 1946.

INDICATIONS FOR THE THERAPEUTIC LAMELLAR CORNEAL GRAFT

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The lamellar corneal graft, in my opinion, has three indications: (1) Optical, in the case of superficial lesions occupying only a part of the corneal thickness; (2) preparatory, in the case of serious lesions of the cornea with dense, highly vascularized leukomas, with a view to preparing the cornea for a perforating graft; (3) therapeutic, that is to say, for the treatment of progressive corneal diseases.

The trophic action in keratoplasty is one of the most interesting phenomena observed after corneal grafting. Judging from the condition of the patient's eye 6 or 12 months after the operation, the improvement of the diseased cornea around the graft is such that, at times, an uninformed observer wonders whether the operation was really indicated.

Filatov is one observer who has laid particular emphasis on the remarkable trophic action of corneal grafting.

For the past 18 months, I have been practicing therapeutic lamellar grafting in diseases of the cornea. Some 40 cases have thus far been observed with results which, in my opinion, are quite interesting.

Therapeutic lamellar grafting may be performed either on the periphery of the cornea or in the center, according to the case and the size of the lesion. Such grafting is indicated in all forms of chronic or recurrent keratitis when (1) all the usual treatments give no results, (2) the center of the cornea is in danger, or (3) a perforation of the cornea is to be feared.

Best results have been obtained in keratitis caused by a neurotropic virus, especially herpes simplex or zoster, in deep syphilitic or tubercular keratitis, or in any keratitis of indefinite etiology.

I have operated upon certain cases of traumatic keratitis, of postoperative dystrophic keratitis, and of ulcerative keratitis. In three cases, it was possible thus to stop a perforation of the cornea; in another, I was able to effect healing in a few days in an abscess of the cornea with hypopyon which had resisted both local and general treatment.

Therapeutic lamellar grafting is an entirely safe operation. In one case out of 10 I have had to perform a second graft to get some results. The lesions often show very fast improvement in 15 to 30 days. The pain stops, the inflammatory signs and ulcerations decrease, and there often is a very high clarification of the cornea. Eighty percent of the cases have shown complete recovery, while the rest have shown improvement. Never have I encountered any accidents or any aggravations of the disease.

Such therapeutic grafting, therefore, is a primary indication for keratoplasty and is at least as useful as optical grafting, if not more so. It actually amounts to a preventive treatment of corneal blindness.

Filatov has especially recommended it in the treatment of disease of the graft in corneal transplantation. He has shown that small lamellar grafts made in the vicinity of the diseased graft may clear up the condition.

Although I have used this technique in a number of cases, in only two have I been so fortunate as to see the disease of the graft decrease. In most cases, the operation comes too late and the opacification of the graft continues. It would seem that a disease process in the graft depends, above all, upon the condition of the eye operated upon; disease is by far less frequent in the healthy cornea and in leukomas with low vascularization. It is easier to prevent dis-

ease of the graft than to cure it. One must strive, at all costs, to improve the condition of the eye in those cases of unfavorable prognosis which have now become familiar to us.

Therapeutic grafting is indicated in all cases where there are only superficial lesions of the cornea and when good visual results can be obtained without undue risks for the patient. Of course, similar results can be obtained by using the perforating-graft technique but with greater risks for the patient. While the indication is clear with totally blind patients, it is necessary to be much more careful with those still having a visual acuity of one twentieth or one tenth. For those with some vision, lamellar grafting can be proposed with great security.

Lamellar keratoplasty is also indicated when the patient is high strung or anxious; in patients with nystagmus; and especially in the patient with only one eye. In an aphakic eye, with vitreous humor in the anterior chamber, only lamellar grafting can be successful.

As has been mentioned, excellent results have been obtained in cases of hereditary keratitis, in nodular keratitis of Groenouw, and in reticular keratitis of Haab-Dimmer. Good results have been obtained in 90 percent of the cases. Among the various forms of corneal degeneration, lamellar grafting gives good results in the fatty dystrophy of the cornea and primary chronic edema.

Successful results may also be obtained in the cases of opacities following infectious keratitis; in Hutchinson's keratitis; in tubercular, eczematous, or rosaceous keratitis, and in keratitis caused by a neurotropic virus. Cases of superficial leukoma following ulcers also give favorable results.

If the associated infection is carefully eliminated, lamellar grafting may be very helpful in cicatricial trachoma. In cases of foreign body in the cornea (following explosions in mines, chemical burns, and so forth) the results often are not so good. However, although other procedures may be necessary, lamellar grafting improves conditions for a subsequent perforating graft. Favorable for lamellar corneal grafts are those cases of keratitis in war patients who were injured by yperite.

Out of 270 lamellar grafting operations performed by me, both successful and unsuccessful, 75 percent had transparent grafts and favorable functional results.

The balance of these cases revealed, in back of the corneal graft, some opacification of the layers of the diseased cornea. In some cases, during the course of the following months, the transparency improved because of a trophic action of the graft, and the functional results also showed progressive improvement. When the amount of vision obtained is not sufficient, a perforating graft may be performed under better circumstances, upon a cornea which therapeutic corneal grafting has greatly improved.

Preventative lamellar grafting, either partial or total, may also be used in performing an iridectomy, an iridosclerectomy, or an operation to liberate the eye from an adherent leukoma of a highly diffused, dense, and vascularized nature. If the lamellar graft loses its clarity, then the perforating graft is sure to fail.

One must be able to repeat such preparatory grafting in order to pave the way for a successful central perforating graft. In cases of chemical burns, in deep, highly vascularized keratitis, and in trachoma, also, this procedure provides an indispensable precaution. In this respect I have obtained satisfactory results.

In short, lamellar grafting in its threefold indication—optical, therapeutic, and preparatory—is one of the most useful means of treating corneal opacity.

Every one of us must work to improve these methods that still are rather new, with a view to obtaining more and more satisfactory results. If the lamellar graft loses its clarity, then the perforating graft is sure to fail.

EXPERIMENTAL CORNEAL GRAFTS OF THE LAMELLAR PARTIAL TYPE*

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The purpose of the experimental surgery performed in this study was twofold. First, to determine the effect of direct edge to edge suturing of partial lamellar grafts; second, to devise a method, if possible, of overcoming the herniation of the recipient bed encountered in lamellar partial transplants. All grafts studied were of homoplastic character on rabbits.

The multiplicity of sutures that have been used to hold the transplanted corneal graft tissue in its bed suggest the conflicting opinions of various authors as to what is the ideal type. Historically, the first attempt to suture a nonpenetrating corneal graft in place appears to have been by Muhlbauer[1] who, in 1840, won a prize offered by the medical faculty of Munich. Other than that he used a triangular-shaped graft held by a single suture at the apex, the exact suture type has not been identified. The result, however, was unsatisfactory.

Durr[2] had performed lamellar grafts, probably the first attempted on human beings, even before von Hippel (1888) published his work on the nonpenetrating graft. Unfortunately, he worked only with peripheral opacities and endeavored the heteroplastic transplant of dog cornea to man. He attempted to hold his triangular graft in place with sutures at the corners, with the main sutures actually in the sclera.

Various methods of holding the graft in its bed have been used through the years. As far as suturing is concerned, however, it has always been of a bridging type. Some sutures have been placed from limbus to limbus, as described by Paufique;[3] others from cornea across to cornea fairly close to the trephination, as used by Paton[4] and others.

The decompression procedure in corneal lamellar grafting is a much more recent refinement. Paufique[3] appears to have made the first reference to this technique which is a definite contribution to successful lamellar-type corneal grafting. The experimental attempts to dispense with this additional procedure will be discussed later.

EDGE-TO-EDGE ALL CORNEAL SUTURE EXPERIMENT

TECHNIQUE.

Anesthesia. A basal anesthesia of intravenous veterinary nembutal was given (0.12 mg. per pound of animal weight). After a few minutes, so that the animal could be prepared and placed on the Katzin[5] operating table without incident, pontocaine (0.5 percent) drops were instilled in the eye to be operated, and one cc. of one-percent novocain was injected, retrobulbarly.

Preparation. The long guard hair about the eye was cut and the area was painted with 1:1,000 aqueous zephiran solution.

Surgery. Lid sutures were used to secure the lids to the drape about the eye, since they were found to be less cumbersome than a speculum. The eye was then fixed by inserting episcleral sutures at the 4- and 8-o'clock positions at the limbus and tying them radially to the drape. Fixation at the 12-o'clock position was maintained with forceps. Both the donor and the recipient animals were prepared in this manner before any corneal procedure.

The recipient cornea was operated first so that the donor graft disc would be out of the corneal environment for a shorter time. With a Paton 5.0-mm. trephine, with the guard set at 0.5 mm., the recipient cornea was cut with oscillating movements of the trephine. The depth of the incision was

* This work was done under a fellowship from the Eye-Bank for Sight Restoration.

further checked with the tip of an iris repositer until a full half-millimeter cut was insured. The disc was then grasped at the 6-o'clock position with a fine iris forceps, and the cleavage plane was followed with a round-tipped No. 14 Bard-Parker scalpel until the disc was free. The disc was then discarded and the recipient bed was covered with a pledget of cotton soaked with normal saline to retard drying.

The donor disc was then removed from the other animal after similar preparation and anesthesia. With a 5.0-mm. Paton trephine, with the guard set at 0.5-mm. depth, the donor cornea was incised using the oscillatory movement. The depth of the cut was checked with an iris repositor tip. When the desired depth had been reached, a single-armed, 6-0 black silk suture was passed from the epithelial surface, just within the graft margin, through the disc till it emerged at the very bottom of the trephine incision (6-o'clock position). The suture was used for elevation as the disc was separated with a No. 14 Bard-Parker blade.

The donor disc was taken directly to the recipient bed and the suture already in place in the graft was continued from the base of the trephine cut out through the recipient corneal epithelium, about 0.5 mm. from the margin. Thus, the graft is sutured edge to edge with the sidewall of the recipient bed.

Next, the opposite suture at the 12-o'clock position was placed in a similar manner, the suture at the 6-o'clock position acting as counter resistance and reducing the handling of the graft by forceps. A fine iris forceps was carefully used to hold the graft when being transfixed by the needle, if the opposite suture was overstrained. The sutures at the 3- and 9-o'clock positions were then placed in the same way. This produced a four-point attachment of the graft, edge to edge with the recipient stroma. Lid sutures of 4-0 black silk, mattress type, were placed. Penicillin ointment and atropine-sulfate (one percent) solution were instilled, and the lid sutures were firmly tied.

The suture placed before the corneal disc is freed performs two functions in addition to elevation and traction. First, it identifies the 6-o'clock position on the graft so that the same corneal fiber relationship can be maintained when the graft is placed in the recipient bed. The value of such relationship may be disputed but it would seem that to use such a suture is to reduce the variables. Of more practical importance, it immediately and always identifies the epithelial surface of the graft. It is extremely difficult to determine which is the "right side up" of a lamellar graft after it has slipped from a transferring spoon. It is true, of course, that the graft will generally curl with the epithelium out but this may not always occur. In any event, the suture prevents such as mishap as putting the graft in place up side down.

Results

Transplantations were performed in the manner described on 10 rabbit eyes which were enucleated to provide histologic sections of the grafts. Enucleations were performed at one hour and at 1, 2, 3, 4, 5, 7, 8, and 10 days after the operation.

One hour postoperative. Graft was already slightly edematous; epithelium of graft and nearby recipient cornea was absent. Some notching was seen between the graft and recipient edges.

One day postoperative. Graft was edematous and a deep gaping notch existed between graft and recipient corneal edges. Recipient epithelium not within the notch (fig. 1).

Two days postoperative. Graft was in place but a notch persisted. No epithelization of graft was seen.

Three days postoperative. Areas of healing of base of the graft to bed were seen; good edge to edge closure on one side, but a notch was on the opposite side and it was epithelized.

Four days postoperative. Recipient bed

was not completely epithelized. Graft too thick in this instance for bed depth.

Five days postoperative. Graft was not present; recipient bed was almost completely epithelized.

Seven days postoperative. Graft was sloughing and only a minute portion survived against the recipient stromal edge. Notch walls were completely epithelized.

Fig. 1 (Shafer). A 5.0-mm. graft implanted in a 5.0-mm. bed, at 24 hours after operation. Full-thickness edge of recipient stroma (C) is separated by a wide, gaping notch (N) from thick edematous lamellar graft (G) sandwiched on recipient bed (B). Graft is thicker than desirable but is in good position and in good approximation to the bed. Epithelization has not progressed to notch, as yet.

Eight days postoperative. Small portion of the graft existed only at margin where there was very little notching. Rest of graft was absent and the base sloughing.

Ten days postoperative. Bed was totally epithelized. A small necrotic portion of the graft was present at the margin right at a suture point; none elsewhere.

Comment

The sections indicate that within one hour after transplantation the recipient stroma and the donor graft are separated by a notch which later becomes epithelized. In as much as corneal tissue is believed to derive its nutriment by diffusion from the periphery, any isolation of a portion of the cornea by an epithelized notch should result in degeneration of the isolated zone. This is apparently precisely what happened. In no instance in over 80 serial sections showing notching (which occurred in all cases), did the graft persist longer that the fifth postoperative day. The only instances of graft material surviving longer than five days were in those sections which were immediately within the suture loop—thus, only in those areas where edge to edge stromal contact persisted.

In order to confirm the status shown on the fifth postoperative day, in which there was almost complete epithelization of the recipient bed, the experiment was repeated. Serial sections of this eye showed a graft residue that had lost most of its corneal histologic characteristics and was overlying an almost completely epithelized recipient bed.

The results of this experiment indicate:

1. The edge-to-edge suture does not maintain approximation of the edges of the lamellar graft and the recipient stroma.

2. Graft survival without edge-to-edge approximation is apparently hindered and it cannot be assured by edge-to-edge sutures.

3. The recipient bed is almost completely epithelized, if a graft is not going to "take," at about the fifth postoperative day.

Experiment on graft shrinkage

These findings suggested further study. The questions posed were: Did the normal intraocular pressure herniate the thin residual cornea and Descemet's membrane of the recipient bed, causing the notching and thus preventing the edge-to-edge approximation necessary for graft survival? Or, did

the graft shrink in size with the same result?

On the predication that shrinkage might be the cause, an experiment was set up so that a larger diameter graft would be placed in a smaller diameter recipient trephination. This increase in the graft diameter appeared necessary to attempt to fill the notching after the edematous stage had subsided.

A size differential of one full millimeter was selected because the notch totalled about that amount in the histologic sections studied in the first experiment.

In order to keep all variables as small as possible, the only difference in technique in this experiment was that the donor graft was cut with a 6.0-mm. trephine, while the recipient bed was still incised with a 5.0-mm. instrument. Using this size difference in each instance, homoplastic grafts were performed on rabbits, and the eyes were enucleated so as to provide histologic sections of the status at 1, 3, 5, 7, and 10 days after operation.

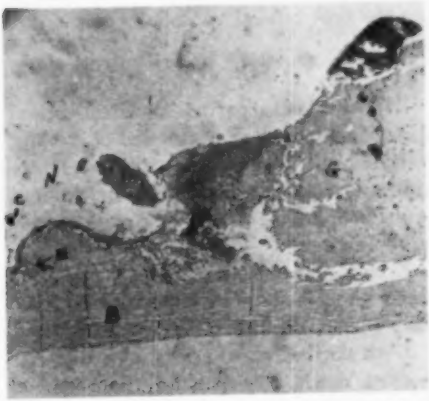

Fig. 2 (Shafer). A 6.0-mm. graft implanted in a 5.0-mm. bed, at five days after operation. Demonstrates wide notch (N) between very edematous graft (G) and corneal wall of recipient bed (B). Note also that epithelium (E) covers entire notch at this stage.

Results

One day postoperative. The 6.0-mm. graft was found to be very edematous and the margins were overriding the recipient cornea; the graft was snugly in place and there was some piling up of the epithelium at the juncture. No notching was seen.

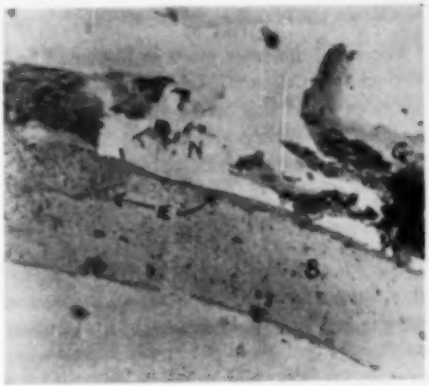

Fig. 3. (Shafer). A 6.0-mm. graft implanted in a 5.0-mm. bed, at ten days after operation. The excluded degenerating graft (G) may be seen lying in the recipient bed (B) with its entire nutriment supply blocked by the complete epithelization (E) of the notch (N) and the recipient bed.

Three days postoperative. The slides showed the graft partially dislodged, but in one slide about 50 percent of the graft was present in the bed. Although the section had been torn, a notch was evident. It was epithelized.

Five days postoperative. The slides showed the graft in place with a wide epithelized notch on one side and a small notch on the other (fig. 2).

Seven days postoperative. The sections showed the graft firmly in place but with overriding and mushrooming of the graft onto the recipient cornea. There was no notching and there was beginning epithelization of the graft surface. This represented the only eye in which the graft appeared to have "taken" in toto.

Ten days postoperative. The slide showed the degenerating graft in a bed which was completely epithelized, including the suture tracts down into the deeper recipient stroma (fig. 3).

Comment

The large diameter graft in the small bed produced epithelized notching in all but two instances—one day after operation, when the graft was very edematous; and in the sections for the seventh postoperative day.

Discussion

The experiments suggest that the edge-to-edge suture is deficient because there was not one instance of a successful graft when both graft and recipient trephination were the same in size.

Theoretically, such a suture should provide the best approximation of the graft to the recipient stroma; however, in every instance of the same size graft as bed, the result was a lost graft and notching. Several slides showed viable fragments of the graft enclosed within the suture loops. Thus, either the graft must have shrunk or torn free, or the bed must have enlarged until the graft could not survive because the epithelium followed the notch down to the base of the bed and then along the bed, isolating the graft.

Since the first reaction of the graft is edema, the idea of shrinkage is probably erroneous. The opposite theory is more tenable—namely, that the bed enlarges. This would adequately explain the notching seen on all of the standard-size grafts, and it would account for the loss of all grafts after the fifth postoperative day when epithelization of the bed is apparently complete.

The attempt to overcome the notching by using an oversized graft was successful in two instances. However, since the larger grafts tend to override onto the recipient cornea, it would be undesirable, optically and subjectively, to use them in operations on human beings.

An alternative procedure must, therefore, maintain the normal diameter of the recipient bed without herniation. To do this, two procedures would appear to be indicated: (1) A bridging suture designed to resist the stretching process of the intraocular pressure; or (2) decompression of the globe at the time of transplantation. (Or, a combination of the procedures.)

Despite the fact that the firm stroma-to-stroma sutures used in these experiments could be tightened as much as a bridging suture, the serial sections made one hour after transplantation showed that notching was already present. It might be that bridging sutures alone would prove inadequate, at least in the relatively soft and thin cornea of the rabbit.

In addition, in the actual operative technique, it was found that the 6.0-mm. graft fitted into the bed cut with the 5.0-mm. trephine without overriding. Thus, the herniation or stretching of the bed must take place during the actual operation itself. In this instance the bridging type of suture would not resist the stretching, for enlargement of the bed takes place before any suture can be tightened.

It would seem, therefore, that a decompression procedure would prove of value in lamellar type corneal transplantations in rabbits.

Summary

1. Homoplastic partial lamellar corneal transplantations were performed on rabbits, using edge-to-edge corneal sutures. Histologic sections were made after enucleations at one hour and 1, 2, 3, 4, 5, 7, 8, and 10 days postoperatively.

2. No standard-sized graft persisted longer than the fifth postoperative day and the recipient bed was epithelized at that time.

3. All standard-sized grafts showed an epithelized notch between the recipient and donor stromal edges, believed due to stretching of the recipient bed.

4. A second series of partial lamellar corneal transplantations were performed with the donor disc one mm. larger in diameter than the recipient bed. Corneal sections made at 1, 3, 5, 7, and 10 days postoperatively were studied.

5. In spite of the use of an oversize graft, a gap or notch was present in all sections but those made on the first and seventh postoperative days.

6. The stretching and herniation of the recipient bed is not resisted by edge-to-edge corneal sutures and is believed to occur during the operation before any retaining suture can be closed.

7. A decompression procedure is suggested to prevent herniation of the recipient bed in lamellar corneal transplantations, at least in the soft cornea of the rabbit.

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Discussion

Dr. Joseph Laval (New York): I should like to ask Dr. Shafer a question: Did the notch appear clinically, or was it seen only after the eye was removed and fixed?

Dr. Shafer: Both, but more so after the eye was removed and fixed.

Dr. Laval: The reason I ask you, Dr. Shafer, is this: Dr. Paufique and Dr. Sourdille showed us lamellar grafts that they did with such beautiful results, and in your lamellar grafts you had notching. My impression was that the notching only occurred because the fixing fluid had shrunk the graft away from its bed and that it really was not a poor operation. I felt that if the eye had been left alone, the graft would have taken, but the fixing fluid pulled it away.

Dr. Shafer: The only thing that tends to indicate otherwise is that a 6.0-mm. graft, cut right on the operating table, will fit readily into a 5.0-mm. bed. My belief is that the stretching occurs as soon as the trephine goes through to the recipient bed.

I noted in the films that Dr. Paufique and Dr. Sourdille presented that they were using a decompression procedure though I did not hear very much discussion about it in their lamellar cases.

Dr. Paufique: When I saw Dr. Shafer's slides, I was amazed to see how prominent was the notch, because in the human eyes after my operation I rarely see such a notch. I think the curvature of the rabbit cornea is very different which may account for this notching.

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PATHOLOGY OF REMOVED CORNEAL SECTIONS

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During the past three-and-one-half years, we have examined 1,088 eyes in the Eye-Bank. Of these, there were:

Normal	930
Papilledema	3
Sarcoma of uveal tract	59
Glioma of retina	7
Epibulbar carcinoma	1
Meningioma of optic nerve	1
Leukemia	7
Glaucoma	41
Uveitis (anterior and posterior)	25
Intraocular hemorrhage	13
Sympathetic inflammation	1
	1,088

In cases of corneal transplantation, degenerative changes develop in the nerves of the host cornea and of the graft. In the host cornea, the nerves degenerate in an area two mm. wide around the graft; these changes are the result of direct action of the trauma exerted on the nerves by the cutting instrument; they follow a course more rapid than that in the graft itself.

Innervation of the graft is accomplished by nerve fibers which sprout from the scar in the host cornea all around the graft. These new fibers, passing across the scar at the junction of the graft and the host cornea, invade the graft and reinnervate it, restoring its sensitivity.

We have been examining the discs of recipient corneas sent to the laboratory with the idea that, from the pathologic changes in the various layers of the recipient cornea, we can determine which factors will influence "a take."

We have found the corneal epithelium changed in each of its five layers, but mostly in the columnar cell layer and in the outermost flattened layer which may at times be keratinized. Bowman's membrane has been found to be absent or else quite thickened or irregular in diameter. The stromal fibers are irregularly placed and the fixed cells and the wandering cells are usually increased in number. Occasionally small blood vessels are found in the corneal stroma. Descemet's membrane and the endothelium are absent, as a rule, having been lost when the disc was removed from the recipient's cornea.

Dense and diffuse corneal opacities have an unfavorable influence on the results of operation. The reasons why corneal grafts fail to remain clear in completely opaque corneas are not fully understood. One explanation which has been given for the poor results in this type of cornea has been that there are not enough normal corneal cells surrounding the graft. This explanation is probably not correct, however, for clear transplants can be obtained in corneas in which all of the original cells have been destroyed by freezing, if sufficient time is allowed for corneal edema to subside and new cells to grow in.

The recipient cornea should not be completely opaque and should not be edematous. Small blood vessels in the recipient cornea are not detrimental to the final clarity of the transplant. After the graft has been inserted, it becomes edematous during the first 24 hours and the epithelium is lost. The endothelium is always damaged to some extent, but part of it may remain on the graft.

The majority of the stromal cells continue to live in the graft and do not show a massive degeneration or replacement at any time during the postoperative course. They are supplemented, at least to a limited extent, by newly formed keratoblasts from the recipient's cornea. The epithelium is replaced by a migration of epithelium from the recipient cornea. The endothelium may be repaired from the uninjured cells of the graft or by a migration of cells from the recipient cornea. The wound is closed at first by a

fibrin clot and later by fibroblasts which form fibrous tissue between the graft and adjacent cornea.

We are trying to correlate the changes in the recipient's cornea with the degree of successful take. We hope, in the future, to have some more definite conclusions.

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SOME OBSERVATIONS ON EMBRYONIC CORNEAL TRANSPLANTATION

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Our work was organized to contrast the healing of embryonic corneal tissue transplanted to animals of the same and different species. For the homologous series, 9- or 10-day-old chick embryo corneas were carried into adult chicken corneas; and 18-day-old rabbit embryonic corneas into adult rabbit corneas. Heterologous transfers were carried from guinea-pig embryos to rabbits; from chick embryos to rabbits; and from 3- and 4-month-old human embryos to rabbits.

Grossly, the transplant is faintly hazy and membranous; it exhibits marked adhesiveness at its edges. Microscopically, its bulk consists of numerous parallel bundles of nucleated cells bounded on each side by a single layer of flattened epithelium. It resembles, in structure, the abdominal wall of the early embryo. The size of transplants varied from about one mm. in diameter of the 18-day-old rabbit embryo to 4.0 or 4.5 mm. of 9-day-old chick embryos.

An optimal age for embryonic tissue was found for heterologous transplants. The reason for this was that, if the curvature of the embryonic cornea was already established when carried to an adult of a different species, it would form a vesiclelike structure. This did not happen in the homologous transplants.

One theoretical disadvantage of embryonic cornea is the absence of Descemet's membrane and the protection which it affords. However, other embryonic tissues grow well in the anterior chamber without benefit of Descemet's membrane, although a good vascular supply is essential. Cases with minimal trauma have been selected for this report and haziness is graded clinically from 1 to 4 plus.

Since there was no essential difference between the homologous and heterologous transplants in the manner of healing, both are treated together in our description.

OBSERVATIONS

In general, all embryonic transplants become opaque by the second or third week. During the first week an elevation or depression of the transplant is frequently noted, due to the marked difference of thickness of the two tissues. A proliferation of the marginal squamous epithelium is frequently seen. This tends to smooth out the surface unevenness. The anterior chamber becomes reëstablished within one week. A marked tendency to adhesions may prolong the period of clearing.

As healing progresses, a faint but definite haze appears in the peripheral incisional zone; while in the clear central area, a small nipplelike projection is frequently noted. The latter represents numerous growing embryonic squamous epithelial cells. Sections at this stage show a proliferation of the epithelial layer, some 8 to 10 cells thick, with an irregular surface and with numerous cystic spaces. New proprial cell bundles are seen extending in parallel bundles. In a few cases, a marked disarrangement of these fiber bundles has been noted. An occasional capillary bud is present.

Microscopically, at about three months, the adult recipient cornea has begun to envelop the embryonic transplant with a new epithelial outer covering and a new endothelial lining. Within the transplant are seen large pale-staining coalescent cells, cellular debris, and numerous small wandering cells loaded with pigment granules. The epithelial layer has become more even, thinner, with an occasional necrotic cell. The anterior layer of proprial cells has become more compact; the posterior group more fibrillar and branching. Descemet's membrane appears to be split or reduplicated. New endothelial cells are seen extending over the entire inner surface.

In order to test the theory that the transplant serves merely as a mechanical bridge for the host's cells, four transplants were placed with the endothelial surface facing outward. All four eyes healed well after a slightly more stormy postoperative course than occurred in the other animals. Although the number of cases is too small for any final statement, the experiment would seem to suggest that the transplant serves mainly as a mechanical bridge.

In some cases we have noted uveal tissue growing actively in the host corneal stroma. Obviously, this was derived from embryonic tissue inadvertently carried over with the transplant.

Six to eight months postoperatively, the transplant becomes quite thin and infiltrated with small wandering cells. The few fibrotic bundles are irregularly arranged, and an occasional capillary is present. The inner portion consists of numerous delicate fibrillas. The epithelium is scanty or missing, a condition caused by the abnormal attachment of epithelium to substratum.

The whole complex structure consists of at least three types of cells: (1) The persistent and/or dead cells; (2) the fibroblasts; and (3) the newly formed cells—the new proprial fibrillas, the new endothelial and epithelial cells—and an occasional blood vessel.

Transplants carried from rabbit embryo to adult rabbits seemed to do best, clearing in about 4 to 6 months with 1- or 2-plus haziness. The next best results were in the group of chick embryo to adult rabbits. These transplants cleared in about 12 to 15 months with 1- or 2-plus haziness. Strangely, the homologous transplants of chick embryo to adult chicken did not clear beyond 2- or 3-plus haziness in eight months' time. Of the four transplants of human fetus to rabbits, one became opaque in six weeks and remained so for about eight months; the second became infected; and the other two are slowly clearing after a 10-month observation period.

Conclusion

Embryonic corneal tissue, on transference, grows moderately well, persists for several months, regresses and dies, and finally is replaced by the cells of the host.

Perhaps the most important factor to consider in experimental corneal transplantation is not how many cases are done but the length of the period of observation.

THE ULTIMATE FATE OF THE GRAFT

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INFLUENCE OF RELATIONSHIP

The success of tissue grafting depends, among many other factors, on the relationship of the graft to the host. When I say relationship, I mean it in its strictest sense. Transplantation from one individual to himself is the most successful form. When such accidental factors as excessive trauma, hemorrhage, infection, and debilitating states are eliminated, this form of transplantation is most uniformly successful. In transplantation to an identical twin the percentage of success falls in the same class with autografting. When a tissue is grafted from one individual to another, the success of the graft depends upon how closely the individuals are related. When a great number of transfers of this sort are done, for example, in small experimental animals, a statistical study can be made and the results of such studies will show:

1. The percentage of "takes" is highest (next to autografts) when the subjects are from closely inbred strains. Since these animals are derived from successive generations of inbred litter mates, their chromosome characteristics approach those of identical twins. It is in these groups that the graft has the best chance of survival.

2. When ordinary litter mates are used for these studies, the percentage of successful takes is lower. Siblings that are not derived from inbred strains may be, by chance, closely related (so far as their gene similarity is concerned) but the statistical treatment of such experiments shows a smaller percentage of successful grafts.

3. When unrelated members of the same species are used, the percentage is correspondingly lower.

4. When tissues are transplanted from one species to another, grafts are not accepted.

NATURE OF TISSUE USED

The next consideration in successful grafting is the nature of the tissue used. Some tissues are relatively resistant and some are very susceptible to the injurious influences involved in tissue transplantation. To take an extreme example, the anterior horn cells of the central nervous system or the ganglion cells of the retina are not suitable for transplantation at all. Interruption of their normal blood supply for a very few minutes causes the cells to die. Cartilage and perichondrium are good materials for grafting because of their relatively small need for nutrition, because of the large proportion of intercellular matrix, and because of the low vascularity.

Cornea is, in some respects, similar to cartilage. The grafting qualities of other tissues, such as skin, endocrine glands, bone, muscle tissue, blood vessels, and blood, lie between the extremes already mentioned. Because of the nature of the tissue reactions involved, these organs respond differently to a change in their environment.

TISSUE REACTIONS

Although the tissue reactions occurring at the site of a transplant follow a pattern which varies with these different factors, a general description would be:

First, the body fluids of the host exert an injurious effect on the graft which varies with the degree of relationship of the graft to the host. These effects can be shown in a number of ways, but to take an example: if a skin graft from a mouse is embedded subcutaneously in a frog, for a very few hours, it will be cast off when returned even to the same mouse. The body fluids of the

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frog have altered it in a subtle but very powerful way, so that it is no longer acceptable to the mouse. The effect of the body fluids is to cause severe cellular damage from which the transplant may not recover.

Second, the fibrous tissue of the host develops about the graft and surrounds it. The amount and permanency of the connective tissue depend upon the acceptability of the graft. The connective tissue may be so extensive as to choke off the nutrition of the graft and cause delayed death. This is the form of reaction frequently seen about a cartilage graft from an unrelated donor. Blood vessels accompany the connective tissue, and the factors already listed will determine whether the fibrous tissue and the blood vessels will form a framework that will nourish the transplant or a capsule that will cause necrosis.

Third, the action of the cellular elements of the blood supplements the action of the body fluids and the fibrous tissue. There are always a few polymorphonuclear cells at the site of transplantation. Their number depends on the degree of tissue damage. They are more abundant when a graft is being rapidly destroyed. Statistical studies in animal grafting experiments are necessary to rule out the effect of infection in the presence of many polymorphonuclear cells. There are always lymphocytes and other mononuclear leukocytes at the transplant site. Their numbers depend likewise on the acceptability of the graft. In large numbers they indicate a milder form of nonacceptance.

In an autograft, there is a migration of blood vessels and connective tissue toward the graft site where they form a loose meshwork. A few lymphocytes may be seen in the connective tissue. In the course of time, the fibrous framework of the graft becomes displaced and is replaced from the host. The amount of connective tissue formed, in general, is very small and, in a few weeks' time, the graft assumes the appearance of the normal structure.

In the case of grafts derived from sources which are less closely related, the injurious effects of body fluids, connective tissue, and leukocytes assume more importance the greater the dissimilarity.

Other factors to consider

The influence of hormones. Hormones may effect the success of a graft. By stimulating growth processes in the graft, they may tend to neutralize the damaging action of the host on an unrelated graft. By depressing growth processes, the effect of unrelatedness may be intensified. Grafted tissues that respond to the action of hormones are, of course, the only ones that can be shown to exhibit these properties.

Blood groups. It has often been asked whether blood groups have any effect on the relatedness of individuals within the same species. There is no definite correlation between the compatibility of blood and skin grafts in the same individual.

The effect of immunity on the acceptance of a graft. Experimental studies reveal that the reactions against grafts from unrelated individuals differ qualitatively as well as quantitatively and that the normal immunity reactions against strange proteins may develop in the case of the transplant. The immune reactions are, however, secondary and participate to a lesser extent in throwing off a strange transplant.

The special case of blood vessels and nerves. Grafting experiments on these tissues have shown that it is possible to obtain a clinically successful result. These results have been hailed as evidence of the transplantability of these tissues. However, closer examination showed that the vessel or the nerve served merely as a framework for the development by the host of its own replacement parts.

The anterior chamber of the eye as a site for tissue transplantation. This locale has been shown to be a particularly successful site for transplantation, especially for the organs of internal secretion. Compared with other sites, diminution is noted in the intens-

ity of both the connective-tissue reaction and the lymphocytic reaction against the transplant.

Intraocular transplantation of malignant tumors may often be shown to take and maintain continued growth. The degree of success seems to depend upon the original growth energy of the tumor.

In the anterior chamber there is a paucity of protein so that immune reactions, as well as the injurious body-fluid response, is less marked. The normal acellularity and lack of connective tissue in the anterior chamber are also factors which are favorable. Pieces of cornea transplanted into the anterior chamber in the same species have been recovered after months, clear and intact, but covered by a layer of endothelium. The anterior chamber is, in many respects, a modified tissue-culture chamber.

The effect of age. Grafting experiments in general have shown greater success in young hosts than in older ones. This has not been borne out to any significant extent, however, in the case of the cornea. So far as the question of the age of the donor is concerned, transplants from very young donors may succeed better than older ones. The individuality differentials are fully developed even in new-born animals so that the greater success enjoyed by these tissues as donors must be due to the greater growth momentum of younger tissues and perhaps, also, to their greater adaptability to unfavorable environmental conditions. In the case of cornea obtained from new-born or still-born donors, the tissue is much more friable, thinner, and more difficult to work with than adult cornea. This material can be used but has to be relatively fresher because it will remain in good condition only half as long as adult corneal material.

Multiple transplantations. Serial transplants, using the same graft from one animal to another, have been done with cartilage in rats. A single graft has been kept alive much longer than the average life span of the rat. We have not tried this type of experiment with the cornea but, on the basis of our experience, there is every reason to believe that it would succeed.

General observations

In the first days after a corneal transplant, a considerable amount of edema occurs at the cut edges. This edema involves the host as well as the donor graft and, in the soft sclera of the rabbit, the edema involves practically the entire globe.

The epithelium of the host proliferates and fills in the gap between graft and host and fibrin fills in the posterior margin. When the donor cornea is very fresh, the epithelium of the graft also proliferates, but we believe that this epithelium is ultimately lost and replaced entirely by the host. Sheets of epithelium are desquamated during the first two weeks of the postoperative period. We believe that the endothelium is replaced by the host in the same manner. Proof of this is, however, more difficult to obtain.

Bowman's membrane of the graft persists. It is not regenerated, and any defect is filled in partly by fibrous tissue and partly by epithelium. The stroma appears to remain unaltered. When the epithelial and endothelial seal is complete, the edema of the stroma gradually subsides and it begins to assume a normal appearance.

Descemet's membrane remains largely unchanged but there may be evidences of regeneration of this structure on the part of the graft. These evidences do not necessarily imply regenerative processes in the graft. It is likely that the endothelium dies soon after enucleation, and that the raw surface of the graft is covered very quickly by the endothelium of the host. Apparently Descemet's membrane is accepted by the host's endothelial cells, because we rarely see a reduplication of Descemet's membrane. However, at the edges where the new endothelium may come in contact directly with corneal stroma, splayed-out fringes of regenerated Descemet's membrane can be seen.

It is apparent, therefore, that all cellular

elements of the graft which are readily replaceable undergo quick substitution by the host. The noncellular elements remain. There is no question that Bowman's membrane remains, and there is little question that Descemet's membrane remains.

The stroma too almost certainly remains. What happens to the stromal cells? In this respect, the cornea bears a great similarity to cartilage which has a paucity of cells in relation to the amount of matrix. The metabolic activity of the corneal stromal cells is very low, but these cells must be replaced from time to time in the normal course of their activity. In the normal adult cornea, it may take years for any significant proportion of them to die and be replaced.

After a transplant operation, replacement takes place much more rapidly, and we believe that the clinical success of a transplant depends upon the rapidity with which this process occurs. If the cells of the graft should die too rapidly for orderly replacement, a slight translucent edema occurs. This edema gradually becomes more marked and remains. This condition occurs when a graft is used that has been kept too long. Histologically, a layer of fibrous cells underlies either the epithelium or the endothelium or both.

If the patient's cornea has a sufficient number of normal corneal cells in the graft bed, these may slowly proliferate and enter the new structure and take over their function in it. When the host's cornea is badly scarred so that few normal cells remain, the graft will not remain clear for more than a few weeks. When the host's cornea is badly vascularized so that reparative processes proceed at a very rapid rate after transplantation, even though there may be many normal corneal cells in the bed, the graft is invaded by connective tissue and does not remain clear.

In short, our concept of successful corneal transplantation is that the donor cornea is a framework which the host's cornea gradually fills in with its own cellular elements while maintaining the original matrix.

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SOME DYNAMIC ASPECTS OF TISSUE STRUCTURE IN CORNEAL EPITHELIUM*

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Some of the most essential factors in determining success or failure in corneal surgery are related to the complex problems of viability of tissue, of wound healing, and of compatibility of tissues. I do not have, before this forum, to review the criteria which are applied in analyzing a given clinical situation from the diagnostic and prognostic viewpoint.

As to the procedures and criteria which the pathologist applies, some of the preceding discussions have illuminated his methods of analysis. From the standpoint of classic pathology, the observed phenomena may be classified as degenerative, proliferative, and inflammatory ones in manifold combinations and successions and involving numerous tissue components.

The preceding discussions have made it clear that the pathologist is no longer satisfied with observing and classifying some final histologic picture. He also endeavors to reconstruct the sequence of events and the role played by different tissue elements, by reviewing synoptically the individual histologic pictures of a clinical or experimentally produced succession of stages. The classic, predominantly descriptive approach is being replaced to an ever greater extent by an approach in which an attempt is made to interpret observations of histologic structure in a dynamic way.

In this approach, structural peculiarities of normal tissue and deviations from normal structure of cells and tissues are viewed as results of processes rather than as isolated static situations; this helps to break down the barriers between pathology and physiology and to obtain some insight into the action mechanisms which lead to morphologic manifestations.

What appears to be of particular importance, in this trend toward a dynamic interpretation of morphologic manifestations, is the fate of the single cell both as an individual entity and as an integral part of an organized tissue. I should like here to illustrate this approach and its implications for the understanding of both physiologic and pathologic phenomena in the tissue by a few examples taken from observations on corneal epithelium.

While corneal epithelium may a priori appear to be of relatively little interest in connection with corneal surgery, it is known from the work of other investigators to have great importance in the exchange of water[1] and of some essential metabolites[2] and thus in the physiology of the cornea. In addition, there is no obvious reason why similar principles and methods should not apply to the stroma as well; an approach which, in fact, has already been considered in some investigations on stroma cells.[3]

OBSERVATIONS ON CORNEAL EPITHELIUM

1. The first example concerns the cellular damage due to ultraviolet irradiation and to mustard and related substances. With appropriate doses of these agents, a peculiar mode of nuclear damage, nuclear fragmentation, develops within several hours and leads eventually to cell disintegration. This phenomenon has been previously described in detail.[4, 5]

Apart from the fact that with mustard the extent of this kind of cell damage is most marked in the basal layers of epithelium, while with ultraviolet it is more marked in the upper layers, the morphologic picture is very similar in both conditions, and so are

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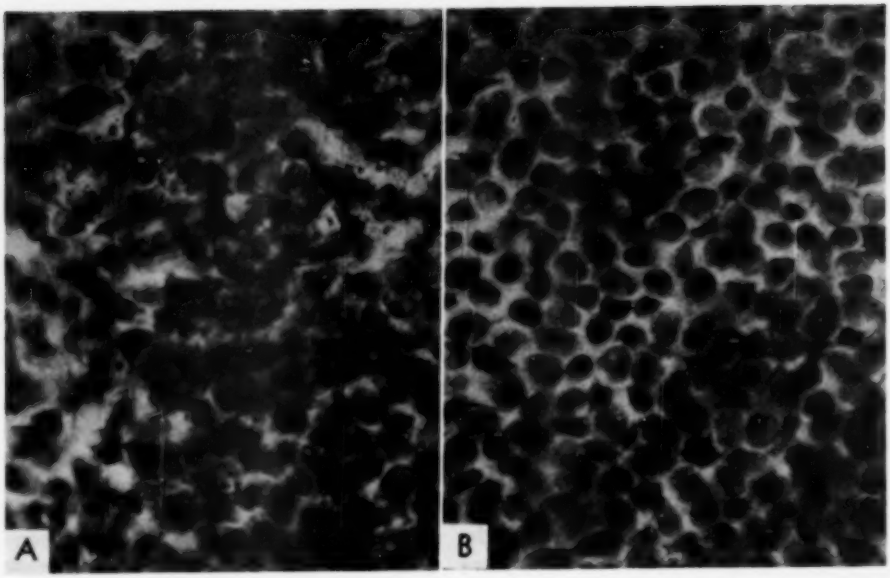

Fig. 1 (Buschke). Effect of temperature on manifestation of nuclear fragmentation following exposure to ultraviolet rays. (A) Incubation for eight hours at 30°C. (B) Incubation for eight hours at 10°C. (Reprinted with permission from the *Journal of Cellular and Comparative Physiology.*)

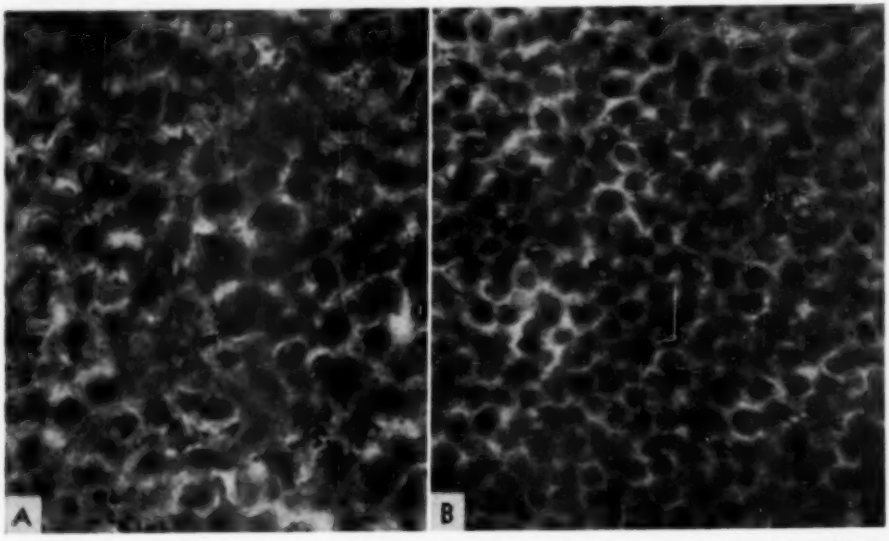

Fig. 2 (Buschke). Effect of anaerobiosis on manifestation of nuclear fragmentation following exposure to ultraviolet rays. (A) Aerobic incubation for six hours at 38°C. (B) Anaerobic incubation for six hours at 38°C. (Reprinted with permission from the *Journal of Cellular and Comparative Physiology.*)

some of the physiologic factors involved in the pathogenesis.

Nuclear fragmentation develops also in vitro; that is, in the corneal epithelium of enucleated eyes which had been exposed to either of these two agents and subsequently incubated in a moist chamber. It was thus possible to study the effect of some environmental variables in vitro.

Changes of temperature have a most pronounced effect. At a temperature of 38°C, the pathologic manifestations develop after 4 to 6 hours, while morphologic integrity is well maintained for much longer periods of time at lower temperatures (fig. 1). The latent period is thus inversely related to temperature with a temperature coefficient (Q_{10}) of about 3.5.

From the standpoint of the mechanisms involved, this is of particular significance in the case of ultraviolet-ray damage; for here no chemical agent is primarily added, the interaction of which with some component(s) of the tissue could conceivably require higher temperature.

It is, therefore, to be postulated that metabolic processes in the tissue itself are responsible for the pathologic manifestation. Of what nature the mechanisms may be which, under normal conditions, prevent, counteract, or compensate those metabolic processes, is unknown at the present time. But it may be considered as certain that, in the development of the damage, enzymes are involved which are part of the metabolic equipment of the cell itself.

It is conceivable and, in fact, quite likely that the same principle applies likewise to the mechanisms involved in the nuclear damage following exposure to mustard, and possibly also in the pathologic conditions of cells and tissues due to a great number of other noxious agents which require a temperature-dependent latent period for manifestation of the damage.

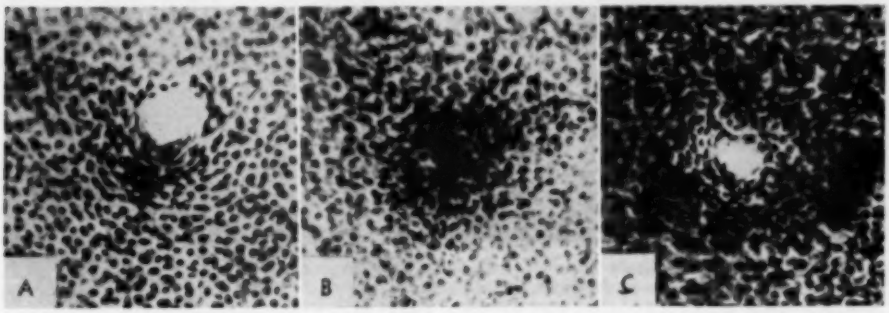

Fig. 3 (Buschke). Temperature dependence of posttraumatic cell movements in corneal epithelium. (A) Fresh pin-prick injury. (B) Similar lesion following three hours' incubation at 38°C. (C) Similar lesion following eight hours' incubation at 21° C. (Reprinted with permission from the *Bulletin of The Johns Hopkins Hospital.*)

Nuclear disintegration, for example, which follows arrest of mitosis in metaphase under the influence of colchicine, has a similarly high temperature dependence.[6] In the cases of ultraviolet irradiation and mustard, in addition, aerobiosis was found to be a requisite for the manifestation of nuclear fragmentation (fig. 2).

2. The healing of epithelial wounds may serve as a second example illustrating dynamic aspects of tissue structure. The most widely used approach to a study of epithelial wound healing is that in which measurable changes in the size of a defect following injury are recorded over a period of time and under exposure to various agents. In order to reduce the number of

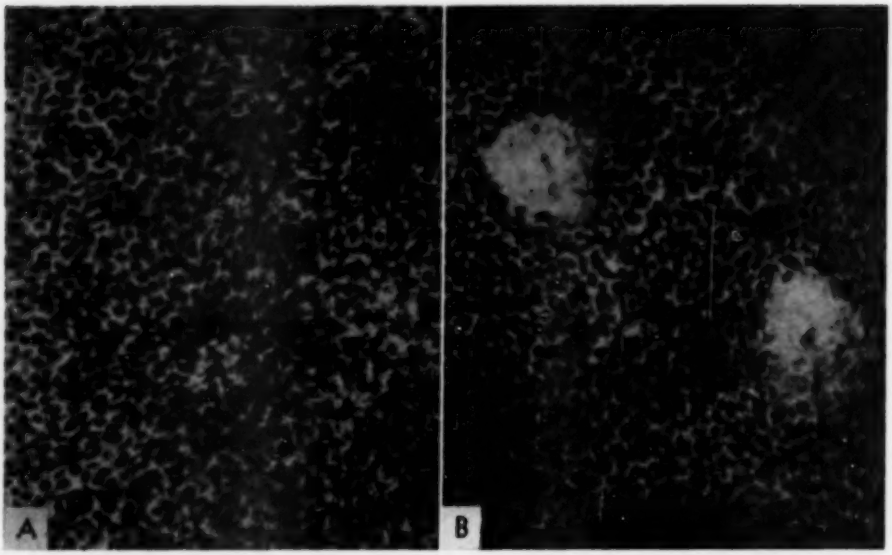

Fig. 4 (Buschke). Inhibitory effect of cyanide on the posttraumatic cell movements in epithelium. Incubation for three hours at 38°C. in (A) Phosphate buffer, pH 7.4, and (B) M/1,000 cyanide in phosphate buffer pH 7.4. (Reprinted with permission from the *Bulletin of The Johns Hopkins Hospital.*)

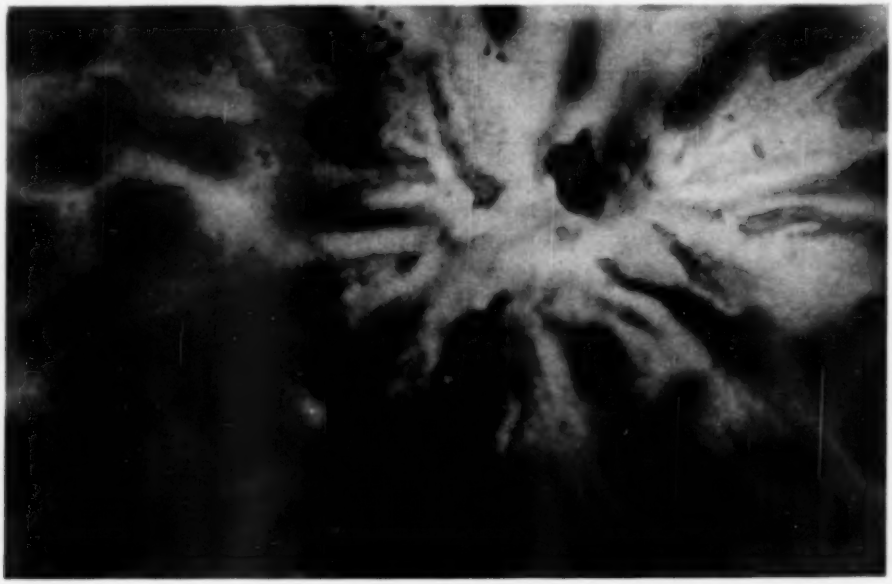

Fig. 5 (Buschke). Pseudopodial cell movements in corneal epithelium in healing of pin-prick injury. (Reprinted with permission from the *Archives of Ophthalmology.*)

variable factors in the experimental approach, a study of the cellular events taking place in the surrounding of very small injuries was initiated, and an attempt was made to use these morphologic observations on the cellular level in assaying the effects of variables applied over shorter periods of time.[7] It was hoped to reveal with this approach some of the dynamic aspects, and

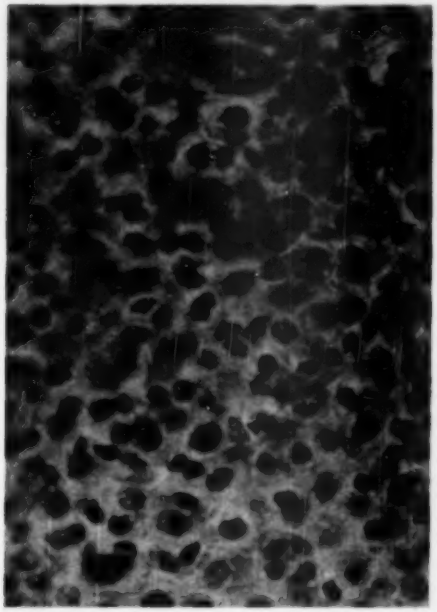

Fig. 6 (Buschke). Control sheet of corneal epithelium following incubation of cornea for 16 hours at 38°C. No loss of cohesion.

thus of the mechanisms, involved in healing of epithelial wounds.

Pin-prick injuries to corneal epithelium heal with cell movements of the surrounding epithelia, and in this process pseudopodial cell extensions play an important role[8] (fig. 5).

3. A study of the variables which would interfere with these cell movements revealed that this phenomenon is highly temperature dependent ($Q_{10} = 5$)[7] and is susceptible to interference by anaerobiosis,[7] cyanide, iodoacetate,[7] and other sulfhydryl binding substances,[8] as well as to that by local anesthetics[7] (figs. 3 and 4).

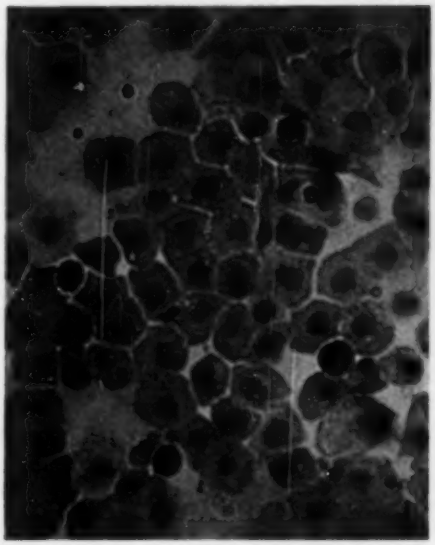

Fig. 7 (Buschke). Loss of intercellular cohesion in sheet of corneal epithelium following incubation for one hour with 2.5 mg. percent chymotrypsin.

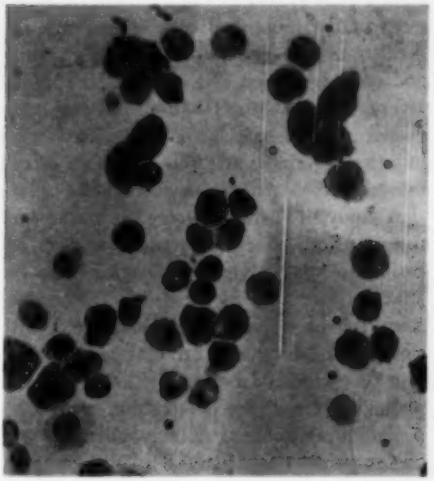

Fig. 8 (Buschke). Loss of intercellular cohesion following incubation of epithelium for two hours with 2.5 mg. percent chymotrypsin.

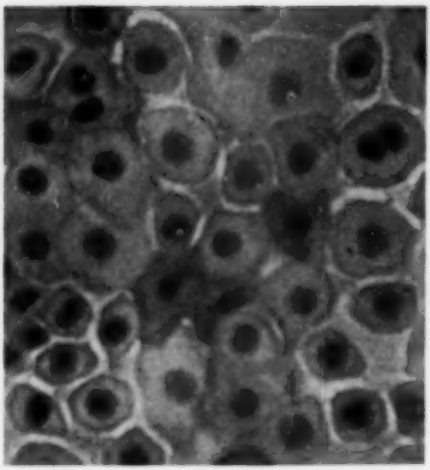

Fig. 9 (Buschke). Loss of intercellular cohesion following incubation of cornea with M/7 fluoride for six hours at 38°C. (Reprinted with permission from the *Journal of Cellular and Comparative Physiology.*)

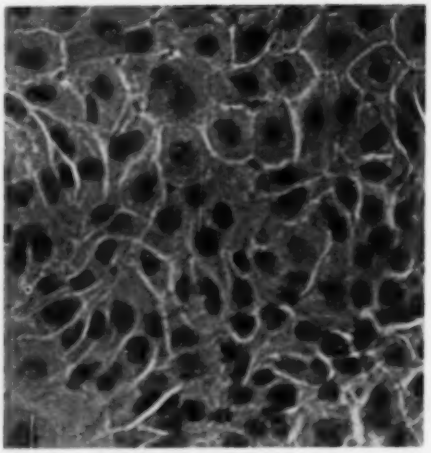

Fig. 10 (Buschke). Loss of intercellular cohesion following incubation of cornea with M/100 iodoacetamide for six hours at 38°C.

In addition, however, this approach revealed some differences in the mode of movement of the individual cells which were dependent on the size and shape of the injury, and on the location of the cell in the multilayered epithelium. These differences suggested that intercellular cohesion may be an important variable affecting the mode of cell movement.[9]

A study of factors involved in tissue continuity or cell cohesion provided another occasion to apply dynamic viewpoints to the study of structure in the tissue. Among the most potent agents which interfered with tissue continuity and brought about isolation of epithelia from each other in a morphologically well-preserved state, were some proteolytic enzymes, notably chymotrypsin and trypsin[10] (figs. 6 and 8).

It was suspected, therefore, that intrinsic proteolytic enzymes of the tissue itself might be responsible for physiologic and pathologic variations of cell cohesion. Under conditions of rest and in a normal organized tissue like that of corneal epithelium, the effect of intrinsic proteolytic activity may not manifest itself in an overall loss of cohesion, because of restraining or compensating metabolic processes.

It is now known from other tissues, however, that the proteins of the tissue, even the structural ones and those considered as most stable, are actually in a steady flux of breakdown and resynthesis.[11]

In applying this line of thought to the problem of intercellular cohesion, the assumption was made that such a steady state of processes of synthesis and breakdown would also prevail in respect to proteins involved in cell cohesion. It appeared likely that metabolic energy would be required for the processes of protein synthesis. Interference with certain energy-producing or energy-transferring metabolic pathways in the tissue might, therefore, be expected to let intrinsic proteolysis manifest itself in loss of cell cohesion.

Exposure of corneas to fluoride, iodoacetate, iodoacetamide, 2,4-dinitrophenol, 4,6-dinitrocresol, and to some local anesthetics, with incubation at body temperature for several hours lead to a marked loss of intercellular cohesion[12] (figs. 9 and 10). It is of interest that some of these agents are known

primarily as inhibitors of glycolytic or phosphorylative pathways. Under otherwise similar conditions, anaerobiosis and interference with oxidative pathways, such as exposure to cyanide or malonate, had no effect on intercellular cohesion.

Much further work will be required to obtain more insight into the mechanisms of cell cohesion. The observations to date, however, appear to be compatible with the idea that processes of breakdown and resynthesis of the proteins concerned in intercellular cohesion play some role and that factors regulating the extent of these two opposite phenomena of tissue metabolism may be responsible for physiologic and pathologic variations in cell cohesion.

These examples may serve to illustrate the possibilities inherent in an approach which stresses the dynamic state of tissue and cell structure. From the practical standpoint, they demonstrate the possibility of modifying and directing by environmental agents the course of events which are causally related to the maintenance and reëstablishment of functional and morphologic integrity of tissue in prophylactic and therapeutic procedures.

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RADIOTHERAPY FOR THE PREVENTION AND OBLITERATION OF CORNEAL VASCULARIZATION

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The use of radiotherapy to prevent or remove corneal vascularization is based on the production of obliterative endarteritis by exposure of blood vessels to the necessary doses of X rays or radium rays. Radiotherapy may be applied pre- or postoperatively or as the sole method of treatment. The treatment may be prophylactic, that is, given so as to prevent the formation of vessels, or it may be given only after corneal vascularization has become clinically appreciable.

In larger blood vessels, the endothelial lining is the most susceptible of the various coats. Gassman,[1] who observed the first instance of obliterative endarteritis 50 years ago, described the microscopic changes of an artery in an X-ray burn: "Several days after irradiation, the nuclei of the endothelial cells become swollen, protrude into the lumen of the vessel, while the cell body undergoes vacuolization; the swollen degenerated cells either desquamate into the lumen or proliferate, and the vessel becomes obliterated."

One of the most thorough miscroscopic studies of blood-vessel changes after radium therapy was made 25 years ago by Dobrovolskaia-Zavadskaia.[2] She emphasized that vessel damage was especially prominent near foci of lightly filtered radium, that is, where the effect of beta rays was added to that of gamma rays.

Beta rays were used therapeutically to obliterate vessels 20 years ago by Kumer and von Sallmann;[3] they successfully treated pterygia and hemangiomas of the sclera, with the use of a contact beta-ray radium applicator alone. More recently, Iliff,[4] Ruedemann and Glasser,[5] and others used beta rays from radon or radium applicators to occlude vessels nourishing benign lesions in the anterior ocular segment. Thus, Iliff irradiated vessels at the limbus and improved 6 of 9 chronic corneal ulcers secondary to acne rosacea keratitis; he also cured 17 of 18 pterygia with the sole use of his beta-ray applicator. Clara Okrainetz reports 19 cases of pterygium treated in the radiotherapy department at the Manhattan Eye, Ear, and Throat Hospital by beta rays from a new radium-D applicator.*

During the past 14 years, we have administered postoperative roentgen therapy to 40 patients operated for pterygium by Dr. Castroviejo. Many of these patients had been operated on previously and the condition had recurred. In 31 of these 40 patients, the treatment was prophylactic and was administered from 1 to 8 weeks postoperatively. In the remaining nine cases, the treatment was given two weeks to three months postoperatively, at which time a visible recurrence of the pterygium had taken place. Postoperative roentgen therapy was successful in preventing recurrence in 20 of 31 prophylactic cases. In the nine cases in which a visible recurrence had taken place, treatment caused the disappearance in four instances.

Interest in obliterating corneal vascularization by radiotherapy has increased with the greater development of corneal surgery. Owens and associates,[6] in a review of the combined results of 381 corneal grafts done in seven eye hospitals, found that only 36.5 percent of corneal grafts remained clear. They concluded that "the percentage of clear grafts varied greatly with the cause of the corneal opacity."

Preoperative vascularization was one of the important causes of clouding of the graft. Thus, clear grafts resulted in about one half of the cases in which the cornea

* See pages 55, 57, and 58.

preoperatively showed no or slight vascularization; in about one fourth, in which vascularization was moderate. Only 1 in 10 grafts remained clear when preoperative vascularization was extensive.

Other causes of failure to obtain clear grafts were tabulated by Castroviejo.[7] in 1946, and corroborated by Owens and associates in 1948. They postulated criteria which permitted classification of cases into favorable, less favorable, and unfavorable groups.

In an effort to set up prognostic criteria for obliteration of corneal vascularization by radiotherapy, we studied 94 eyes in patients operated on by Castroviejo, as well as some eyes of patients treated in the radiotherapy department of the Manhattan Eye, Ear, and Throat Hospital. Most of Castroviejo's cases were treated by X rays postoperatively; those from the Manhattan Eye and Ear were usually given beta-ray therapy preoperatively. The results of the beta-ray therapy are described in detail by my associate, Dr. Okrainetz.*

Factors influencing outcome

Three factors influenced the outcome of the treatment: (1) The condition of the cornea when treated, (2) the age of the capillaries, (3) and the technique of treatment.

Condition of cornea at the time of radiotherapy

The cases referred to us for postoperative roentgen therapy were usually those which normally tend to vascularize. Thus, cases of keratoconus or small central leukomas were not referred for prophylactic postoperative roentgen therapy, since corneal grafts under these favorable conditions usually remain clear without irradiation. Corneal vascularization, however, did develop in 11 cases of keratoconus, and was obliterated by postoperative roentgen therapy in four of these cases.

Postoperative roentgen therapy was also successful in over one fourth (28 percent) of 77 other cases in which the preoperative diagnosis was corneal ulcer, chemical burn, or unknown cause. The results were best in those cases in which the preoperative cause of corneal opacity was infection and degeneration of the cornea or traumatic ulcer. Corneal vascularization was prevented or made to disappear in nearly two thirds of these cases—in 11 of 17 cases which preoperatively had been classified as due to infection or degeneration of the cornea, and in 6 of 11 cases due to traumatic ulcer.

A keratectomy had been done in 81 instances and a keratoplasty in 38 instances. Prevention or obliteration of corneal vascularization was successful in 40 percent of the keratectomies and 42 percent of the keratoplasties. Apparently the type of operation did not affect the postoperative response of corneal vascularization to roentgen therapy.

Age of capillaries

Since newly formed capillaries consist mainly of endothelial cells, they are especially sensitive to radiation. The older the capillary, the less radiosensitive it is likely to be. One would, therefore, expect that radiotherapy would be more effective as prophylactic treatment soon after excision, when capillaries are just beginning to form, than it would be after they have become fully developed.

Postoperative prophylactic irradiation is started within 24 hours after keratectomy and several days to two weeks after keratoplasty. The delay after keratoplasty is chiefly because of the fear of inadvertent trauma to the graft. Postoperative roentgen therapy for visible vessels is sometimes delayed from two weeks to three months postoperatively, to see if they will disappear spontaneously.

In 75 instances in which radiation was given prophylactically after operation, 33 patients or 44 percent did not develop vascularization postoperatively. It cannot be

* See pages 53 to 56.

claimed that all of these patients would have developed corneal vascularization if they had not been treated. It may be assumed that this would have occurred in many cases, however, for most of the patients referred for prophylactic postoperative roentgen therapy have shown a preoperative tendency to corneal vascularization. In 42 cases there were visible vessels when roentgen therapy was started; in 14 cases, or 33 percent, these vessels were obliterated.

This seems to support the belief that it may be a little easier to prevent the formation of vessels postoperatively than to occlude them after they have become fully developed.

Choice of radium or x-ray therapy

The obliterative endarteritis produced by radium rays and X rays is similar. The depth to which these rays penetrate into the sclera and cornea varies. Most vessels in corneal vascularization are located within the first millimeter below the surface of the cornea. It is, therefore, advantageous to concentrate as much of the radiation in this region as possible. It is also desirable not to allow much radiation to reach the lens, because of the danger of producing a radiation cataract. These two prerequisites are met by several types of radium and X rays.

Radium emits alpha, beta, and gamma rays, which represent, respectively, 90, 4, and 6 percent of the total energy of radium. Alpha rays are absorbed by a sheet of writing paper; beta rays by 0.5 mm. of gold; while the hard gamma rays will penetrate even 25 cm. of lead.

Of the three types of radium rays, beta rays have recently been preferred for the treatment of corneal vascularization. About 60 percent of beta rays applied on the surface of the cornea reach a depth of one mm. Only 10 percent remain at a depth of five mm. Thus, beta rays concentrate at the site of corneal vascularization and are reduced to a minimum at the level of the lens.

A convenient source of beta rays is the so-called radium-D applicator recently used in the radiotherapy department at the Manhattan Eye, Ear, and Throat Hospital and described by Okrainetz. The advantage of the radium-D applicator over the conventional radium or radon applicator is the minimal amount of gamma rays emitted by the radium-D plaque.

The applicator is centered over the vessel at the limbus and held in contact with the globe for the duration of the treatment. If the patient does not maintain the eye in one position, it is best to hold the applicator by hand so as to follow the motions of the eye. If the applicator is in a rigid stand or attached to a lid speculum, the eye may be moved out of the irradiated field, unless constantly supervised.

The chance of trauma from pressure of the applicator on a fresh graft increases with the duration of the individual exposure. Strongly charged applicators like the radon applicator of Iliff have the advantage of short treatment periods. Weak applicators, however, may be used just as effectively if the total dose is split up into several fractions and the shorter treatment is repeated daily until the desired total has been administered. This protracted treatment has the advantage of milder reaction of the conjunctiva; at the same time, it produces as satisfactory endarteritis of the vessels as occurs when the total dose is given by stronger applicators, in one or a few treatments close together.

Severe conjunctival reactions may result if several adjacent fields are treated on the same day; the fields overlap, for the treated area is always a little wider than the radium-D applicator. Another beta-ray source, now available commercially, is an applicator charged with radioactive strontium. We have not had any personal experience with it, but it is said to be satisfactory.

Low voltage X rays differ in their ability to penetrate tissues depending upon the voltage at which they are produced. The voltage varies from Grenz rays, at 10 or

12 kilovolts (K.V.), to other low voltage X rays, up to about 100 K.V.

The rays produced in an X-ray tube consist of a mixture of easily absorbable and penetrating rays. The former are absorbed in the superficial layers of the cornea and sclera, unless previously filtered out by the glass of an X-ray tube; the rays which get out of the X-ray tube may be stopped by the interposition of filters between the X-ray tube and the eye.

Some X-ray tubes, for example, for Grenz rays, have a special window so that even easily absorbable rays may get out of the tube. Beryllium has recently been used as a window for X-ray tubes from 30 to 100 K.V., as it does not stop easily absorbable rays. Filters are unnecessary when treating corneal vascularization, because of the superficial location of the vessels.

The distribution of radiation within the anterior ocular segment from X rays produced at 25 K.V.,[8,10] or those at 30 to 100 K.V.[9] but with a beryllium window, resembles that from a beta-ray applicator; these are best suited for the roentgen therapy of corneal vascularization.

Grenz rays at 12 K.V. do not reach the site of corneal vessels in amounts adequate for obliteration of corneal vascularization. This may be seen from Table 1 constructed by our hospital physicist, Lillian E. Jacobson. This table also shows that, when 45 K.V.[11-13] or conventional glass X-ray tubes up to 100 K.V. are used, the proportion of radiation reaching the lens is considerably higher than when 25 K.V. are used, when a beryllium window is substituted for the glass, or when a beta-ray radium applicator is employed.

We do not employ a filter for treatment of corneal vascularization, although we did use one in a few of the early cases, which we also radiated with higher voltages. For some of the patients, we used 100 K.V., 15 cm. T.S.D.,* no filter. In most, we employed either 45 K.V., 3.4 cm. T.S.D., no filter; or 60 K.V., 10 cm. T.S.D., no filter. The last technique is the one we employ at present.

TABLE 1

COMPARISON OF DEPTH DOSE VALUES FOR DIFFERENT RAYS: PERCENTAGE OF SURFACE RADIATION AT VARIOUS DEPTHS

	mm. Below Anterior Surface Cornea	Beta Rays	Grenz Rays		X Rays (glass tube)	X Rays (beryllium window)	
			12 K.V.	45 K.V. Hvl. 0.3 Al.	100 K.V. Hvl. 0.78 Al.	30 K.V. Hvl. 0.06 Al.	100 K.V. Hvl. 0.08 Al.
			(contact 9 cm.)	(contact 2 cm.)	(contact 15 cm.)	(contact 15 cm.)	(contact 15 cm.)
Post. surf. cornea	1	60	17	95	86	31	34
Ant. surf. lens	5	10		38	57	7.5	12
Middle of lens	7			27	49	4.8	8.1
Post. surf. lens	9			20	43	3.2	6.2

Installation for treatment

With the patient lying on the back, several drops of two-percent pontocaine hydrochloride are instilled into the eye to be treated. The cornea is carefully inspected with an enlarging lens. If vessels are present in only one narrow segment of the limbus or cornea, the X-ray beam is centered over this area. If vessels completely surround the cornea, the entire circumference of the cornea is irradiated in one large area or in several overlapping fields around the limbus.

* T.S.D. = Target skin distance.

Special cones* are used to channel the X-ray beam to the desired area. These cones are made of brass, have an opening of one cm. or less at the distal end, and a much wider proximal opening toward the X-ray tube. The wide proximal opening makes it more likely that the target of the X-ray tube will be centered over the distal opening. The distance from the X-ray target to the distal opening of the cone is 10 cm.

After anesthesia is complete, the lids are separated by a speculum, and the cone of the X-ray tube is lowered to within a couple of millimeters above the cornea. Special care must be taken with keratoplasties so as not to traumatize the graft. Blepharospasm, photophobia, sudden movements of the patient, all make correct installation difficult.

The X-ray beam is primarily directed toward the limbus, although irradiation of a portion of the cornea cannot be avoided. It is difficult to protect that part of the cornea which is free of vessels and does not require irradiation. We have tried to use lead discs over the center of the cornea, but have found them unsatisfactory. Many patients are unable to keep their eye in one position for any length of time and tend to move it out of the field of irradiation.

If part of the cornea is protected by lead shields and the eye is moved the slightest bit, the narrowed field exposed to the X rays makes it more likely that the vessels of the limbus will be outside of the irradiated area. The X-ray exposure takes only a few seconds and the patient can usually hold still long enough for the treatment.

Protection of the uninvolved cornea is nearly as difficult when irradiating with beta rays, except that the irradiated area may be a little narrower.

Dosage

Damage to blood vessels varies with the radiation dose, that is, the amount of radiation reaching the vessel and the time in which this is administered. Damage is marked if the amount of radiation is great and the entire treatment is given in a single exposure. The injury is milder if the amount of radiation is less, or if the total dose is fractionated over several treatments. At first our total dosages did not exceed 600 r; later, however, we gradually raised it to 1,500 r, which remains our usual dosage at present.

When all the cases we have treated are divided into those which received more than 600 r and those which received less than this amount, we find that corneal vascularization was prevented or obliterated in 44 percent of the 83 cases in which the higher dosage was used and in only 20 percent of the 44 cases in which the lesser dosage was used. In seven cases in which there were visible vessels and which received 500 r or less, there was only one instance of obliteration as compared to 12 of 35 cases in which the vessels were occluded when more than 500 r were used. It would seem, therefore, that prevention and obliteration of corneal vascularization is more likely to be successful with X-ray doses which are higher than 500 r or 600 r in air with unfiltered X rays of 45 to 100 K.V.

Of 26 prophylactic cases, corneal vascularization was prevented in 58 percent when dosage varied between 800 r and 2,000 r. This result was obtained in only 41 percent of 49 patients when lesser dosage was used. Castroviejo, who has followed most of these patients, has not observed the formation of a cataract even in those receiving the highest dosage. Nevertheless, we rarely go above 1,500 r with 60 K.V., no filter, 10 cm. T.S.D., and we do not like to repeat the treatment except after an interval of several months when the tissues have presumably recovered somewhat from previous irradiation.

The treatment is usually started with a daily dose of 250 r and then is repeated six times on consecutive days, Sunday excepted, until the dosage is 1,500 r. This daily dose

* These cones are manufactured by B. Odmann of Leonia, New Jersey.

is given irrespective of whether 45, 60, or 100 K.V. are used. It is advisable to start with less dosage if the eye shows marked chemosis of the conjunctiva and the postoperative reaction seems to be acute.

With the 10 mg. radium-D applicator which gives off 200 roentgen equivalents (r.e.) per minute, the usual daily exposure is five minutes for a total of 1,000 r.e. A longer exposure is not tolerated quite so well. The radium-D plaque at the Manhattan Eye, Ear, and Throat Hospital gives off 300 r.e. per minute and five minutes of treatment would result in a dosage of 1,500 r.e. It is difficult to postulate a rigid dosage schedule for beta rays. We have seen vessels disappear after a mere 1,200 r.e. and have seen other vessels remain prominent until 5,000 to 6,000 r.e. had been administered; 6,000 r.e. has been the upper limit usually given to most of our cases treated with the radium-D beta-ray applicator.

Summary

A review of the literature and of our own experience with the use of beta rays and low voltage X rays to prevent or obliterate corneal vascularization leads us to believe that the result of this treatment is influenced chiefly by three factors:

1. The condition of the cornea at the time of irradiation and the preceding cause of the corneal opacity. The results are best if the opacity is due to infection or degeneration of the cornea or to traumatic ulcer. In these cases corneal vascularization may be prevented or obliterated in about two thirds of the cases. If vascularization is due to other causes, the treatment is successful in about one third of the cases. Prevention or obliteration of vessels by radiotherapy is as successful after keratectomy as after keratoplasty, that is, in about 40 percent of the cases.

2. The result is influenced by the age of the capillary. Postoperative prophylactic results are successful in 44 percent of cases; when visible vessels are present, the incident of success is 33 percent.

3. Successful beta and X-ray therapy depend upon adequate dosage. We were unable to establish a definite dosage level at which all vessels would be obliterated. With beta rays this varied from 1,200 to 6,000 r.e., the higher figure being more reliable. With X rays at 45 or 60 K.V., the results were better when a dosage of over 600 r was administered; our average dose was 1,500 r given in one week. The most satisfactory distribution of radiation on the basis of physical measurements may be obtained by the use of beta rays, X rays at 25 K.V., or X rays through a beryllium window with voltages from 30 to 100 K.V. Radiation is thus concentrated in the region of corneal vascularization, yet it is reduced to a minimum at the levels of the lens. Nevertheless, 60 K.V., no filters, 10 cm. T.S.D. has also given satisfactory results without, as far as we know, the production of a cataract.

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BETA IRRADIATION OF THE EYE USING THE RADIUM-D APPLICATOR*

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In the field of ophthalmology, the radiotherapist has always sought a type of irradiation which could be applied with benefit to the superficial structures of the eye without causing damage to the underlying tissues. Grenz rays and the low voltage X rays have been used. More recently beta rays have been tried. Beta rays are absorbed in the first three mm. of tissue and do not penetrate any deeper. It seems, therefore, that beta irradiation is ideal for treating corneal lesions without danger of producing a cataract.

There are several beta-ray applicators in use at the present time. In 1940, Burnham[1] designed an applicator containing radon as a source of beta irradiation. This is the applicator used by Iliff[2] in Baltimore. Burnam's method, however, depends upon access to a large radon plant which is not available to every one. Commercial companies make high charges for supplying a similar bulb.

A new applicator, introduced recently, is supposedly a source of pure beta rays without the admixture of gamma rays. This is the radium-D applicator now used at the Manhattan Eye, Ear, and Throat Hospital. It is made of radium-D which has a half-life period of 22.2 years. According to Professor Evans[3] of the Massachusetts Institute of Technology, this applicator is a source of practically pure Beta rays, since 99.9 percent of the total ionization produced by the ordinary radium-D applicator is due to the beta rays; the feeble gamma radiation present has a quantum energy of only 0.047 million electric volts (Mev).

The radium D is encased in a Monel box, the window of which is 5.6 mm. in diameter and covered with a thin layer, 0.05 mm., of aluminum (fig. 1). This permits a maximum amount of beta rays to emerge from the applicator.

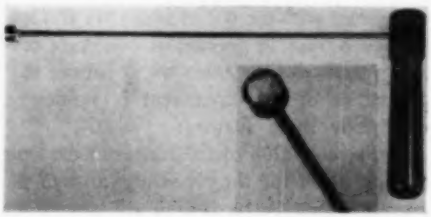

Fig. 1 (Okrainetz). Radium-D applicator.

The applicator, D129, used at the Manhattan Eye, Ear, and Throat Hospital, contains 20 mg. of radium D and was measured by Professor Evans in April and May, 1948.[4] It emits between 18,100 and 18,300 roentgen equivalents per hour, or 300 per minute. A roentgen equivalent (r.e.) may be defined as that amount of beta radiation which, under equilibrium conditions, releases in one gm. of air as much energy as one roentgen of gamma rays.

* From the radiotherapy department and the corneal clinic of the Manhattan Eye, Ear, and Throat Hospital.

After a mild anesthetic is used, the applicator is placed in direct contact with the cornea at the limbus for a sufficient number of minutes to give an average of from 900 to 3,000 roentgen equivalents per treatment, depending upon the lesion to be treated.

Dr. H. M. Katzin and I began using the radium-D applicator on rabbits in March, 1948, at theManhattan Eye, Ear, and Throat Hospital. A dose of about 6,000 r.e. fractionated over three weeks was established as sufficient to obliterate corneal vessels and yet be well tolerated by the surrounding tissues. The radiotherapy department started to use the radium-D applicator clinically in May, 1948.

Beta irradiation is known to be very effective in occluding corneal blood vessels, especially if they are newly formed. This method of treatment proved to be of great benefit in keratoplasties.

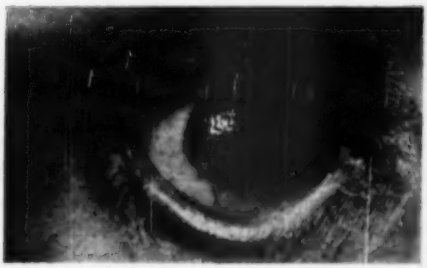

Fig. 2 (Okrainetz). *Case 1.* Before treatment. Corneal opacity with marked vascularization.

Case reports

In the following case of long-standing corneal opacity with vascularization, the vessels were successfully occluded with beta irradiation to the limbus before a corneal transplantation was done.

Case 1

J. I. (No. H-35453). This 38-year-old patient had a lime injury of the right eye of 20 years' duration. When he was admitted on December 10, 1947, the cornea was opaque and vascularized. There were multiple adhesions of the upper eyelid (fig. 2).

Fig. 3 (Okrainetz). *Case 1.* After treatment. Vessels are obliterated at the limbus.

Unfiltered X-ray therapy, (40 K.V., 5 M.A., and 10 cm. T.S.D.*) was first tried in 500 r to 600 r doses twice a week. A total of 3,800 r was given between December 10th and 24th. There was general improvement but the vessels had not changed. Beta irradiation was, therefore, started in March, 1948.

Five fields at the limbus between the 1- and 7-o'clock positions were treated from March 3, 1948, through April 27, 1948. A total of 6,300 r.e. to each of two fields and 3,000 r.e. to each of three fields was given. The eye was then considered ready for keratoplasty (fig. 3) which was done on October 19, 1948. There was no delay in healing (fig. 4—November 1, 1948). This case illustrates that the

* T.S.D. = Target skin distance.

Fig. 4 (Okrainetz). *Case 1.* After corneal transplantation.

Fig. 5 (Okrainetz). *Case 2.* Before treatment. Corneal density with multiple hairlike blood vessels.

rather heavily irradiated surrounding tissues could stand surgery well and that no apparent damage was inflicted on the tissues.

Occasionally the occlusion of the corneal blood vessels causes sufficient clearing of the corneal opacity with resultant improvement in vision, making a corneal graft unnecessary, as illustrated in the following cases. The first is that of a recent injury and the second is of an injury of long standing.

CASE 2

R. M. (No. J-2599). This patient was admitted on February 5, 1948, with a history of lime injury of the right eye in August, 1947. There was a nebulous opacity of the whole cornea, with a dense area in the lower half. There were numerous fine, hairlike blood vessels in the corneal tissue extending to the pupillary area and including almost the entire circumference (fig. 5). Vision in the right eye was 5/200.

The eye was first treated with unfiltered, very superficial X rays, using 40 K.V. and 10 cm. T.S.D. A total of 1,350 r was given between February 5 and 20, 1948. Because no essential change was observed, beta irradiation was started.

Six fields at the limbus were treated between June 14th and July 14th, each field receiving between 1,800 r.e. to 4,200 r.e. As the opacity gradually became thinner, vision improved. On December 28, 1948, vision in the right eye was 20/70; on July 15, 1949, plano, 20/70. At the present time vision in the right eye is 20/50 (fig. 6). Keratoplasty was not considered necessary.

Fig. 6 (Okrainetz). *Case 2.* After treatment. Obliteration of the blood vessels at the limbus with thinning of the opacity.

CASE 3

T. V. (No. H-4579). This patient was referred for obliteration of the corneal blood vessels before a corneal transplantation could be contemplated. He had an aphakia and old corneal injury of the left eye with vascularization of a corneal leukoma. His chief complaints were attacks of photophobia and blurred vision. Vision in the left eye was 3/400.

A brush of vessels came down into the cornea from above and at the 3-o'clock position. The vessels were superficial toward the center of the cornea and deep in stroma toward the periphery (fig. 7).

Beta irradiation was administered to each of two fields at the limbus from the 11- to 12-o'clock and the 12-to 1-o'clock positions. A total of 8870 r.e. was given to each area between April 5, 1948, and May 4, 1948 (fig. 8). Another 3,000 r.e. were given at the limbus at the 3-o'clock position on September 2, 1948 (fig. 9).

The treated areas became avascular and the opacity thinner. The eye became symptom free, "not a bit irritated." The patient could work as a farmer without any photophobia. Vision in the left eye on April 27, 1949, was

20/200 in comparison with 3/400 on admission. Because of the marked symptomatic improvement, keratoplasty in the presence of the aphakia did not appear to be indicated.

Table 1 lists other cases of corneal opacities with vascularization treated by beta ir-

Fig. 7 (Okrainetz). *Case 3.* Before treatment. Leukoma and corneal vascularization with a brush of vessels coming down into the cornea from above and at the 3-o'clock position.

radiation and resulting in obliteration of blood vessels. The amount of irradiation used in our series depended upon the duration of the condition. If the scar and vascularization were of long standing, they required more intensive irradiation. Newly formed blood vessels, on the other hand, were more radiosensitive and responded easily to lower doses. Our tendency now is to keep the total dosage down to about 6,000 r.e. to one field given within about three weeks. In most of

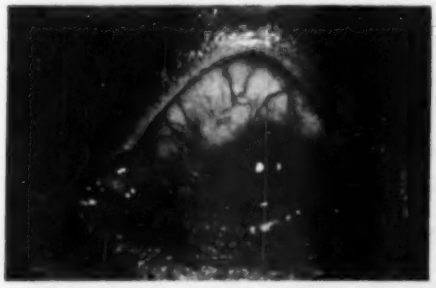

Fig. 8 (Okrainetz). *Case 3.* After treatment. The treated areas became avascular and the opacity thinner.

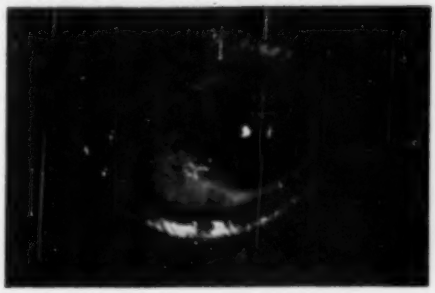

Fig. 9 (Okrainetz). *Case 3.* After treatment. Obliteration of the vessels at the limbus and thinning of the opacity.

the cases this is sufficient to occlude the vessels.

Beta irradiation proved to be of great value in the treatment of pterygia and pseudoptergyia, and, in most cases, made surgery unnecessary.

CASE 4

M. B. (No. J-17765). This patient had a pterygium of the nasal half of the right eye (fig. 10). Three fields were treated between June 28, 1948, and September 13, 1948. One area at the limbus received 6,000 r.e. in two treatments; the second area near the caruncle received 4,500 r.e. in two treatments; and the third area just below the first received 5400 r.e. in two treatments (fig.11). When last seen on January 13, 1949, the result was excellent and surgery was not indicated.

Fig. 10 (Okrainetz). *Case 4.* Before treatment. Pterygium of the right eye.

TABLE 1

CASES OF CORNEAL OPACITIES WITH VASCULARIZATION TREATED WITH BETA IRRADIATION AND RESULTING IN OBLITERATION OF THE BLOOD VESSELS

Name	Age (years)	Date of Admission	Lesion	No. of Treatments and Dosage	Result
H. G.	36	6/17/48	A small area of opacity with vessel, following herpes zoster.	5,400 r.e., 4,800 r.e. and 4,200 r.e. to 3 fields.	Occlusion of vessel.
E. A.	36	6/14/48	Corneal scarring with numerous vessels, due to bombing.	5,400 r.e. and 4,800 r.e.	No follow-up.
A. K.	50	11/24/48	Opacity of upper segment with vessel into it.	1 field: 5,100 r.e.	Vessel obliterated. Opacity thinned.
J. K.	58	1/17/49	Corneal opacity with vascularization. Lye injury.	5 fields at limbus: 6,000 r.e. to each of 3 fields and 1,500 r.e. to each of 2 fields.	Treated vessels obliterated. General improvement.
S. I.	64	2/23/49	Bilateral corneal vascularization. Erythema multiforme 16 years ago.	O.S.: treated at limbus. 4 fields: 3,000 r.e. each, and 2 fields: 1,500 r.e. each.	Improvement in vision. Obliteration of vessels.
M. S.	36	3/ 9/49	Vascularization of cornea since ulcer in October 1948.	1 field: 5,700 r.e.	Vessel obliterated.
A. C.	53	4/ 5/49	Corneal opacity of 30 years' standing. Vessels upper limbus. Irritation of O.D.	3 areas to upper limbus: 5,400 r.e., 3,900 r.e. and 2,700 r.e.	Vessels obliterated. Eye improved considerably.
S. W.	46	5/10/49	Corneal opacity with vascularization. Carbon dioxide injury 12 years ago.	O.S.: 4 fields at limbus: 3,000 r.e. each to 2 fields and 4,800 r.e. each to 2 fields. O.D.: first had a lamellar graft; then 4,800 r.e. to 1 field and 1,800 r.e. to 1 field.	To be followed in the fall.
B. D.	18	7/ 8/48	Adherent leukoma with vascularization.	3 fields at limbus in 2 months: 3,000 r.e., 3,900 r.e. and 5,400 r.e., respectively.	Complete blanching of vessels. Eye ready for transplant.
H. M.	37	12/27/48	Corneal opacity with vascularization. Injury end of July.	3 fields at limbus in 3 months: 5,100 r.e., 6,600 r.e. and 6,000 r.e.	Obliteration of vessels. Ready for transplant.
A. D.	53	12/29/48	Small opacity with vascularization.	1 field at limbus: 3,600 r.e. in 2 treatments.	Improvement in vision.
L. S.	40	12/15/48	Bilateral corneal opacity with vascularization. Injury O.D., April, 1947.	O.D.: 2,700 r.e., 6,000 r.e. to each of 3 fields.	Improvement. Sent home for 6–8 months.
			Totally blind—O.S.: Lamellar keratectomy 12/16/48.	O.S.: 4,500 r.e. to each of 4 fields following keratectomy.	Later a penetrating graft is planned.
J. S.	41	7/ 9/48	Multiple adhesions with vascularization of bulbar and palpebral conjunctivae. Opacity of cornea following injury with sulphuric acid.	2 fields: 1,500 r.e. and 2,400 r.e., respectively.	Improvement.
D. M.	24	10/11/48	Adherent leukoma with vascularization. Lamellar graft.	7,200 r.e. in 3 treatments.	Improvement in vision.
A. J.	39	8/11/48	Bilateral corneal opacity with vascularization. Injury 3 months ago.	O.D.: 6,000 r.e. to 2 fields. O.S.: 3 fields: 6,000 r.e., 1,800 r.e. and 3,600 r.e.	Improvement in vision.
L. G.	56	3/ 2/49	Bilateral corneal vascularization, due to trachoma.	O.D.: 5 fields upper limbus: (1) 6,900 r.e.; (2) 3,000 r.e. to 3 fields; and (3) 2,400 r.e. O.S.: 2 fields; 3,000 r.e. and 2,700 r.e.	Obliteration of vessels.
G. B.	41	9/27/48	Bilateral corneal opacity of vessels.	O.D.: 3 fields at limbus: 5,400 r.e. to 2 fields and 1,500 r.e. to 1 field in 5 weeks.	Vessels disappeared. Lamellar graft, 1/26/49. Penetrating, 4/29/49.
			Graft became cloudy and vascularized.	Additional therapy: 2 fields: 3,900 r.e. and 4,200 r.e.	Partial clearing of graft.
L. K.	49	10/20/48	Keratoplasty 7/19/48. Irritation of eye. Opacity of graft with vascularization, 1 mo.	3 fields to corneal vessels entering graft: 5,700 r.e., 4,500 r.e., and 1,500 r.e.	Last seen on 5/25/49. Improvement. Eye became quiescent.
S. G.	39	8/13/48	Corneal vascularization following transplant for keratoconus, March 1948.	3 fields: 5,400 r.e., 5,400 r.e., and 2,700 r.e.	Occlusion of vessels.
A. O.	48	8/10/48	Corneal opacity; postlamellar keratoplasty.	1,800 r.e. to 2 fields.	No follow-up.
A. N.	49	2/16/49	Corneal transplant 1/20/49. Opacity of upper ridge of graft. Vessel at 3 o'clock.	2,400 r.e. at 12 o'clock; 2,400 r.e. at 3 o'clock.	Improvement. No further follow-up.
A. F.	78	2/23/49	Corneal transplant 1/21/49. Clouding of lower ridge of graft. Vessel at 7 o'clock.	3 fields: 6,000 r.e., 5,400 r.e., and 1,800 r.e.	Treated vessels obliterated.
G. G.	66	4/ 7/49	Fine deep vascularization-argyrosis. Graft 3/2/49. Vessel entering graft.	3 fields: 2,700 r.e., 5,100 r.e., and 3,000 r.e.	Improvement. Blanching of vessels.

CASE 5

J. A. (No. H-24220). This patient was admitted on May 5, 1948, because of pterygium of the left eye of several years' duration (fig. 12). Beta irradiation was given to each of three fields between May 5, 1948, and August 10, 1948. The area next to the limbus received 8,550 r.e., and two areas medial to it received 4,800 r.e. each. The reaction following the treatment was rather mild. Complete clearing of the pterygium was obtained (fig. 13).

Fig. 11 (Okrainetz). *Case 4.* After treatment. The result was excellent and surgery was not indicated.

Fig. 12 (Okrainetz). *Case 5.* Before treatment. Pterygium of the left eye.

When last seen on July 12, 1949, there was no evidence of recurrence (fig. 14).

In cases of pterygia where a recurrence is seen after operation, beta irradiation is especially valuable.

Fig. 13 (Okrainetz). *Case 5.* After treatment. Complete clearing of the pterygium was obtained.

CASE 6

J. M. (No. J-15141). A 25-year-old man was admitted on June 2, 1948, because of a recurrence of pterygium of the nasal half of the left eye. Two removals had been done, one in 1947, and the other in 1948, four months prior to admission (fig. 15). Therapy was instituted, and four fields were irradiated between June 2nd and September 7th. The area over the limbus received a total of 10,200 r.e. in four treatments. The area next to the caruncle received 3,000 r.e. and the other two fields received 4,800 r.e. and 1,800 r.e., respectively. The patient was seen last on October 18, 1948. The result was excellent (fig. 16).

Table 2 shows the results of 16 other

Fig. 14 (Okrainetz). *Case 5.* After treatment. When the patient was last seen, there was no evidence of recurrence of the pterygium.

TABLE 2

CASES OF PTERYGIUM TREATED WITH BETA IRRADIATION

Name	Age (years)	Date of Admission	Symptoms and Duration	Operated	Therapy	Result
C. C.	42	7/ 8/48	Pterygium with irration of eye.	6/24/48	Field: 7,500 r.e. in 3 treatments. Field 2: 4,500 r.e. in 2treatments. Field 3: 3,000 r.e. in 1 treatment.	Excellent.
W. G.	47	5/18/48	Recurrent pterygium of 10 years' duration, O.D.	Cauterized 3 years ago.	3 fields in 2 months. 3 treatments: 3,000 r.e., 3,900 r.e. and 4,200 r.e.	Excellent.
G. T.	49	8/24/48	Thick red fleshy growth nasal half, O.S.	(1) a year ago (2) 4 days ago.	2 fields: 5,400 r.e. and 3,600 r.e. 2 fields: 2700 r.e. each.	Marked improvement.
J. S.	20	9/22/48	Pterygium 7 months' duration.	None	4 fields in 6 weeks: 2,400 r.e., 2,100r. e., 3,000 r.e., and 3,000 r.e.	Excellent.
B. G.	49	11/ 1/48	Recurrent pterygium.	3 times	2 fields: 4,800 r.e. and 2,700 r.e.	Marked improvement.
J. D.	38	12/ 7/48	Pterygium O.S., 4 mos.	None	3 fields: 4,800 r.e., 2,700 r.e., and 2,400 r.e.	Good.
K. B.	51	11/29/48	Bilateral pterygium 8–10 years.	None	O.S.: 2 fields: 6,000 r.e. and 3,300 r.e., O.D.: 1 field: 2,700 r.e.	Marked improvement.
D. H.	23	5/23/49	Pterygium incompletely removed Feb., 1949. Few cysts.	Feb. 1949	2 fields: 5,100 r.e. and 2,400 r.e.	Cysts removed 6/21/49 to speed recovery.
M. F.	30	4/25/49	Pterygium O.S.: few years duration.	None	3 fields: 5,400 r.e., 2,400 r.e., and 1,500 r.e.	Insufficient follow-up.
R. C.	67	3/11/49	Pterygium.	None	2 fields: 5,400 r.e. and 3,000 r.e.	Improvement; no follow-up.
D. H.	53	3/10/49	Bilateral pterygia.	O.S. in Jan. 1949.	O.S. treated: 2 fields: 2,700 r.e. and 3,000 r.e.	No follow-up.
E. W.	40	3/ 1/49	Bilateral pterygia. O.D.: pterygium invading cornea, not highly vascularized.	None	O.D.: 3 fields: 3,000 r.e., 5,700 r.e., and 5,400 r.e.	Marked improvement.
C. G.	38	1/18/49	Pterygium O.D., O.S. removed because of shrapnel injury.	None	4 fields: 5,100 r.e., 4,200 r.e., 3,000 r.e., and 5,400 r.e.	Marked improvement.
J. A.	31	6/10/49	Pseudopterygium outer half O.D., 2 yrs. 9 mos.	Pterygium removed 9 mos. ago. Vascularization cauterized 5 mos. ago.	1 field: 5,100 r.e.	Improvement.
D. G.	46	10/ 7/48	Pseudopterygium	None	2 fields: 2,100 r.e. and 1,800 r.e.	Excellent.
W. H.	37	4/27/49	Pinguecula	None	1 field: 3,900 r.e.	Improvement.

cases of pterygium treated with beta irradiation.

Beta irradiation has also proved to be of great benefit in some cases of chronic corneal ulcers in which stromal infiltrates are present. Deep and superficial vessels from the limbus find their way into these infiltrates. Application of beta rays at the limbus often produces occlusion of the vessels and, with the decrease in vascularity, improvement of the ulcer follows.

CASE 7

F. X. G. (No. J-23996). A man aged 31 years, was admitted to the eye clinic in August, 1948, with a history of corneal ulcer of the left eye of three months' duration. The ulcer developed following a sore throat. He was treated by a private physician with penicillin and tropical applications without any result. When seen at the clinic, the eye looked angry. Ulceration of the center of the cornea with staining was present. Injections of milk were given without any improvement. He was then referred for a trial with irradiation.

When seen in the radiotherapy department in September, 1948, his chief complaints were marked photophobia, pain, impairment of

vision, and excessive lacrimation. He stated that he had not been able to work for about four months. Examination revealed the left eye to be congested. There was deep ulceration of the cornea just below the pupil, with

Fig. 15 (Okrainetz). *Case 6.* Before treatment. Recurrent pterygium of left eye.

extravasation of blood into the cornea and "hipping of tissue" in the pupillary region (fig. 17).

On September 16, 1948, after anesthetizing the eye with pontocaine, the radium-D applicator was applied to the limbus at about

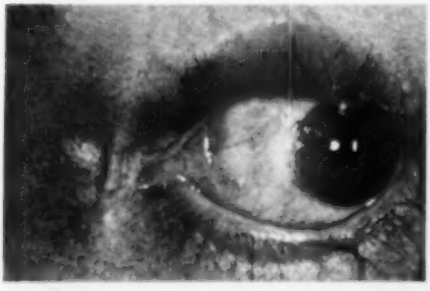

Fig. 16 (Okrainetz). *Case 6.* After treatment. The result was excellent.

the 6-o'clock position for five minutes. About 1,500 r.e. were given to a field 5.5 mm. in diameter. Four days later definite subjective improvement was noted. The pain and lacrimation were less marked and vision seemed to have improved. The ulcer had flattened. The treatment was repeated in a week. Following this second exposure his condition further improved. For the first time in 3 to 4 months, the eye was kept wide open without irritation or pain. The corneal abrasion disappeared. A few dilated vessels were seen in the lower sclera with one single vessel running into the cornea from below at about the 6-o'clock position. This was treated on October 20, 1948, about one month after the first two exposures, and an additional 2,400 r.e. were given (fig. 18). The patient is symptom-free and is back at work. When last seen on May 11, 1949, only a thin opacity was present.

Fig. 17 (Okrainetz). *Case 7.* Before treatment. Deep ulceration with extravasation of blood into the cornea.

CASE 8

A. D. (No. E-4447). A woman, aged 62 years, had had recurrent ulcers of the left cornea since February, 1944. The first time

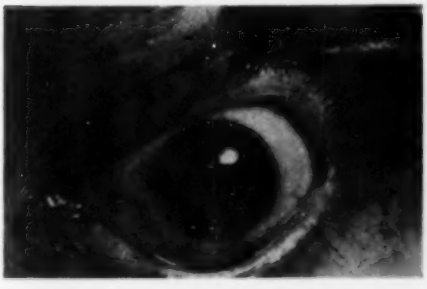

Fig. 18 (Okrainetz). *Case 7.* After treatment. The corneal abrasion disappeared. When last seen, only a thin opacity was present.

Fig. 19 (Okrainetz). *Case 8.* Before treatment. A recurrent dendritic ulcer at about the 5-o'clock position.

she responded rather well to conservative treatment. In May, 1948, a dendritic ulcer appeared at the center of the cornea and persisted for several months in spite of topical, as well as systemic, therapy.

When seen in the radiotherapy department on October 19, 1948, the entire eye was injected. An old scar in the center of the cornea, with a pannus at the upper segment, was present. There was a recurrent ulcer with opacity above it, at about the 5-o'clock position (fig. 19). She complained of pain, photophobia, and lacrimation.

TABLE 3

CASES OF KERATITIS TREATED WITH BETA IRRADIATION

Name	Age (years)	Date of Admission	Duration Before Treatment	Findings: Lesion	No. of Treatments and Dosage	Results
E. C.	49	12/23/48	A few months. Recurrent ulcer O.S.	Keratitis with vascularization at 5 o'clock.	5 treatments to limbus over 5 weeks: 3,900 r.e. total.	Cured. Only slight opacity when last seen 6 mos. later.
M. G.	41	10/ 6/48	Four months.	Herpetic ulcer of cornea, O.D., with vascularization.	2 treatments to limbus in 2,500 r.e. doses over 3½ months.	Cured.
I. F.	56	6/ 8/48	4 months. Corneal ulcer O.D.	Opacity and vascularization.	3 treatments to 2 fields over 2½ weeks: 5,000 r.e. each.	Improvement.
E. W.	51	1/ 5/49	Inflammation on and off 5–6 years O.D.	Slight opacity over pupil Vessel towards it, 7–9 o'clock.	3 treatments over 1 field: 5,100 r.e.	Eye became quiescent.
M. S.	53	3/ 4/49	Iritis and corneal erosion after foreign body injury 3½ mos. Cauterization. Pain.	Indentation at limbus: opacity.	3 fields: 3,600 r.e. in 3 treatments, 3 weeks; 2,100 r.e. in 2 treatments; and 900 r.e. in 1 treatment.	Failure. Eye remained angry and painful.
S. B.	23	3/17/49	8 months' duration of conjunctivitis, followed by scarring of cornea.	Keratoconjunctivitis.Pannus 9–12 o'clock. A few opacities of cornea.	3 areas at limbus: 3,000 r.e., 3,300 r.e., and 3,300 r.e., 3 treatments in 6 weeks.	Improvement. Blanching vessels.
J. D.	30	1/20/49	6 weeks. Corneal ulcer O.D. Failed with conservative treatment.	Ulcer. Vessels at 8–9 o' clock.	3,300 r.e., 3,600 r.e., and 4,200 r.e. to each of 3 fields.	Improvement in vision. Eye quiescent.
S. A.	34	2/17/49	Blurring of vision O.S., 18 months.	Slight opacity upper segment of cornea; interstitial keratitis.	5 fields at limbus: 1,200 r.e., 18,00 r.e., 3,600 r.e., 3,600 r.e., and 4,500 r.e.	Vessels obliterated. No improvement in vision.
J. H.	41	3/16/49	Photophobia and lacrimation O.D. Nov. 1948 and again on 3/9/49.	Opacity of lower half of cornea with ulceration? Vascularization.	1 field at limbus at 6 o'clock: 6,000 r.e. in 3 treatments.	Marked improvement. Opacity thinner.
B. R.	51	10/18/48	Iritis and keratitis O.S., April 1948.	Opacity in pupillary area. A vessel from limbus into it.	At Mayo Clinic: 100 mc. ×83 sec., 100 mc. ×50 sec. in July. At Manhattan Eye, Ear & Throat Hosp., 3 treatments to same field: 7,800 r.e.	General improvement. Vessel still present. In July, 1949; no attacks.
S. V.	49	10/28/48	Pain, photophobia, lacrimation, blurred vision, O.S.	Chronic keratitis with diffuse punctate irregularity of cornea. Vascularization.	3 fields were treated: 3,600 r.e., 5,100 r.e., and 5,100 r.e.	Considerable symptomatic improvement. Deep seated vessels still present.
S. K.		5/10/49	Pain; lacrimation O.S.	Cataract since 1932. Corneal infiltrations and vascularization. ? T.B. keratitis.	2 fields: 5,400 r.e. and 900 r.e.	Considerable improvement. Deep seated vessels visible.
F. O'C.	47	10/20/48	Vascularization with small opacities in cornea, O.S.	Sclerosing keratitis.	1 field: 4,800 r.e.	Vessel obliterated. Opacity unchanged.

After one application of beta rays to the limbus and cornea for six minutes, giving a dose of 1,800 r.e., there was marked relief of symptoms. The eye looked better. With two additional treatments given at 8- to 10-day intervals, the eye became practically normal. She received a total of 4,500 r.e, in 20 days. She has remained symptom-free since her last treatment. Except for a small area of slight opacity, the eye shows no abnormalities. Her vision is 40/70. (fig. 20).

Fig. 20 (Okrainetz). *Case 8.* After treatment. Seven months later, the eye shows no abnormalities and there is only a small area of slight opacity.

In cases of interstitial keratitis treated with beta rays, no appreciable improvement was noted.

Table 3 shows the results of 13 cases of keratitis treated with beta irradiation.

The mode of action of beta irradiation in keratitis is speculative. It has been pointed out that the beta rays increase the antibody reaction in the cornea, and it may be that the beneficial result is obtained in this way. Or, perhaps, the treatment at the limbus produces occlusion of the vessels and, with the decrease in vascularity, improvement follows. Whatever the mode of action, I believe it is worthwhile to try beta irradiation in every case of keratitis when the more conservative treatment fails.

Excellent results have been obtained in vernal catarrh. Recurrences are less frequent and, when they do occur, they are of shorter duration and not so severe.

CASE 9

J. Z. (No. K-14272). This nine-year-old

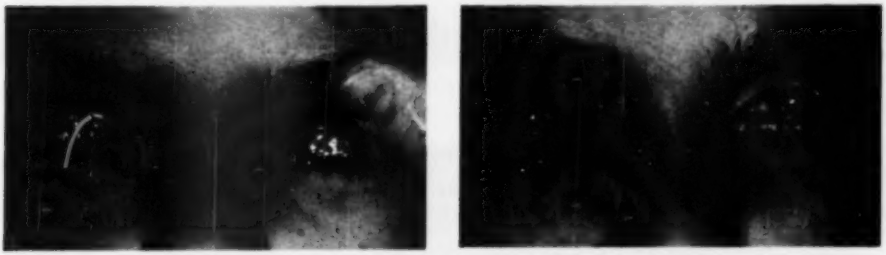

Fig. 21 (Okrainetz). *Case 9.* Before treatment. Bilateral vernal catarrh.

Fig. 22 (Okrainetz). *Case 9.* After treatment. There was marked improvement.

TABLE 4

CASES OF VERNAL CATARRH TREATED WITH BETA IRRADIATION

Name	Age (years)	Date of Admission	Symptoms and Duration	Findings	Therapy	Result
M. G.	11	5/ 4/48	Itching, irritation, discharge 4 years' duration.	Multiple large excrescences of both upper lids.	Prior: Medication. Several operations. March, 1948: X-ray therapy, 900 r.	Marked improvement.
		May, 1948: Exaggeration of symptoms.	Multiple large excrescences of both upper lids.	May, 1948: Left: X-ray, 800 r. Right: Beta rays: field 1: 9,600 r.e., field 2: 1,800 r.e., field 3: 1,800 r.e.	Improvement for a whole year. May, 1949, slight recurrence controlled by adrenalin and drops.
E. V.	8	6/23/48	Itching, watering "thick matter" in the mornings since September, 1947.	Multiple excrescences of palpebral conjunctivas, bilateral.	6/23/48–8/24/48 Right: 2 fields, 11,000 r.e. each. Left: 2 fields, 11,000 r.e. each.	Complete relief of symptoms with flattening of excrescences. May, 1949, mild recurrence of symptoms.
R. H.	9	5/ 2/49	Pain, discharge, and itching on and off for 5 years.	Multiple excrescences of both upper eyelids. Eyes red and congested.	Right: X-ray: 60 K.V., 1,800 r. Left: Beta rays: 3 fields: 2,400 r.e., 2,400 r.e., and 2,700 r.e.	Right: Improved but not completely. Left: Complete relief of of symptoms.

boy was admitted on May 17, 1949, complaining of "running eyes" and itching of two years' duration. Examination revealed excrescences of both upper eyelids, the left more than the right (fig. 21). He was given beta irradiation to the eyelids, protecting the eyeball. Each lid was treated over two fields and received 2,100 r.e. and 1,500 r.e., respectively, between May 17, 1949, and July 28, 1949, in three treatments. When seen last on September 22, 1949, there was marked improvement (fig. 22).

Table 4 lists three other cases of vernal catarrh treated with beta irradiation.

CONCLUSION

In conclusion, the radium-D applicator is an effective source of beta irradiation and has proved to be a valuable adjunct in the treatment of benign lesions of the superficial structures of the eye. In no case treated at the Manhattan Eye, Ear, and Throat Hospital was there injury to the underlying or adjacent tissues.

210 East 64th Street (21).

I acknowledge with thanks the work of Mr. Don Allen, medical photography department, Manhattan Eye, Ear, and Throat Hospital, who made all the photographs for this paper.

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PRESENTATION OF CASES*

R. Townley Paton, M.D.
New York

An attempt has been made, in presenting these cases, to select a few typical cases and also a few cases that, up until recently, were considered inoperable because of complicating factors.

* From Manhattan Eye, Ear, & Throat Hospital.

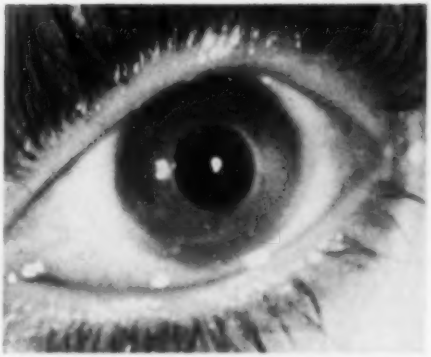

Fig. 1 (Paton). *An amblyopic eye.* Completely scarred cornea, involving all the layers (but no blood vessels present), in which a penetrating corneal transplant has remained clear for three years. Formerly a painted contact glass was used in these cases for cosmetic improvement. In this case, although central vision was not improved, there was a considerable improvement in peripheral vision, as well as cosmetic improvement.

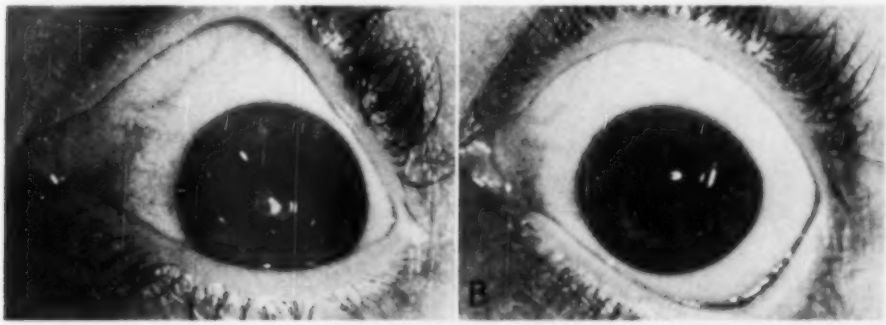

Fig. 2 (Paton). *Conical cornea.* (A) Preoperative vision, with correction, was 20/300. (B) Postoperative vision was 20/20 with a −5.0D. sph. ⌣ −1.25D. cyl.

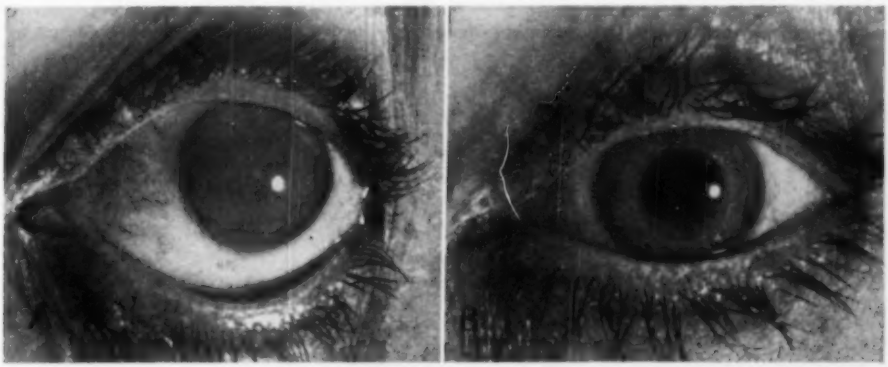

Fig. 3 (Paton). *Groenouw's dystrophy.* (A) Preoperative vision was 2/200. (B) Postoperative vision was 20/30 with correction, following transplantation of a 6.0-mm. penetrating corneal graft. It is usual to find a slight clearing of the surrounding cornea adjacent to the graft in this type of dystrophy.

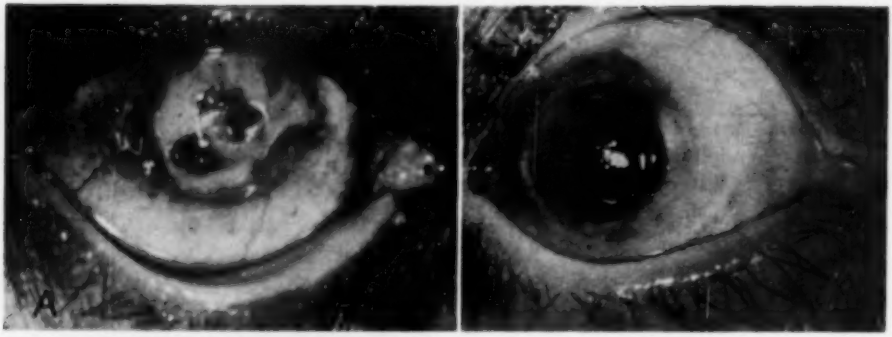

Fig. 4 (Paton). *Completely scarred cornea.* (A) Preoperative vision was light perception. Two previous 5.0-mm. transplants had been unsuccessful. (B) Postoperative vision, six months after a 10-mm. corneal transplantation, was finger counting at two feet. The cosmetic improvement is marked.

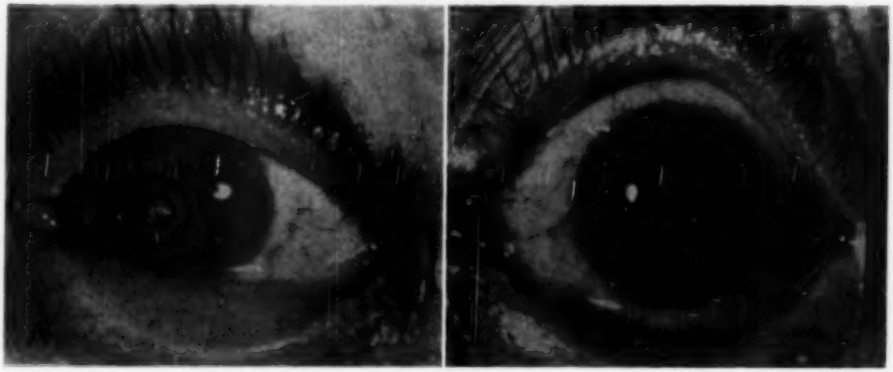

Fig. 5 (Paton). *Superficial central scar.* (A) Preoperative vision was 20/200. The etiology of the scar is unknown. (B) Posttreatment vision was 20/40. Treatment consisted of currettage and application of two-percent hydrochloric acid.

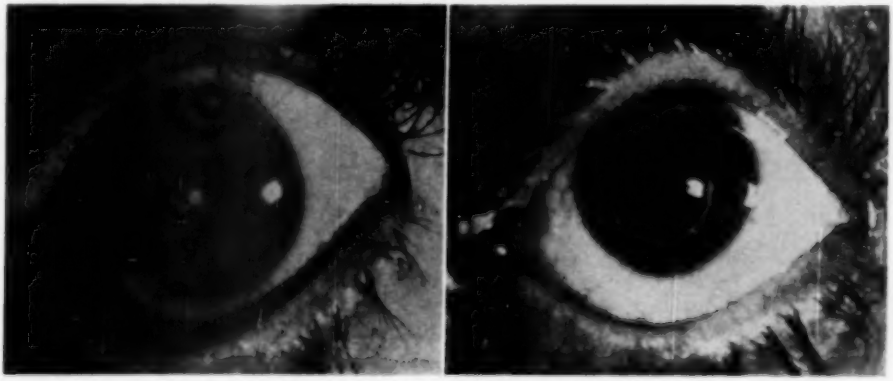

Fig. 6 (Paton). (A) *Old keratitis* (nonspecific in origin) after irradiation therapy for the destruction of small blood vessels. (B) One year after a penetrating corneal transplant, vision was 20/20.

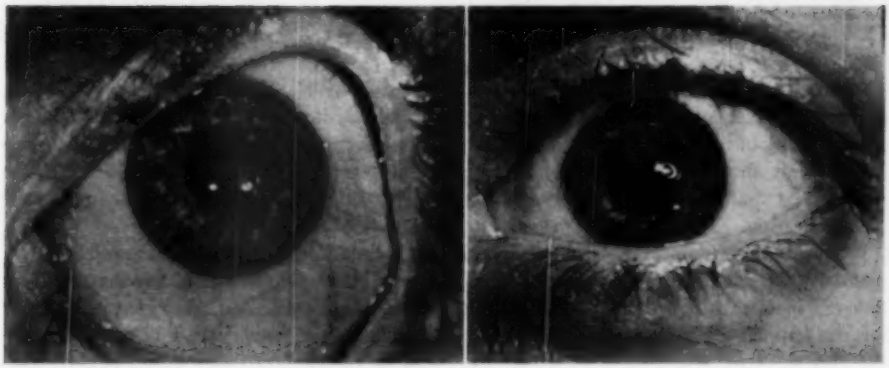

Fig. 7 (Paton). (A) *Conical cornea* after first corneal grafting operation. The graft became cloudy from an unknown cause. No blood vessels were present. Vision with correction was 10/200. (B) One year after the second grafting operation was performed. The graft has remained clear during three years of follow-up. Vision with correction is 20/30.

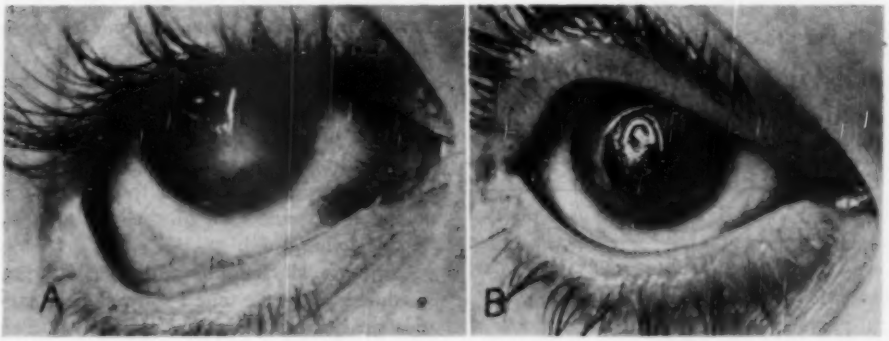

Fig. 8 (Paton). (A) *Adherent leukoma* after beta irradiation to destroy several large vessels at the 6-o'clock position. (B) Postoperatively, there was marked cosmetic improvement.

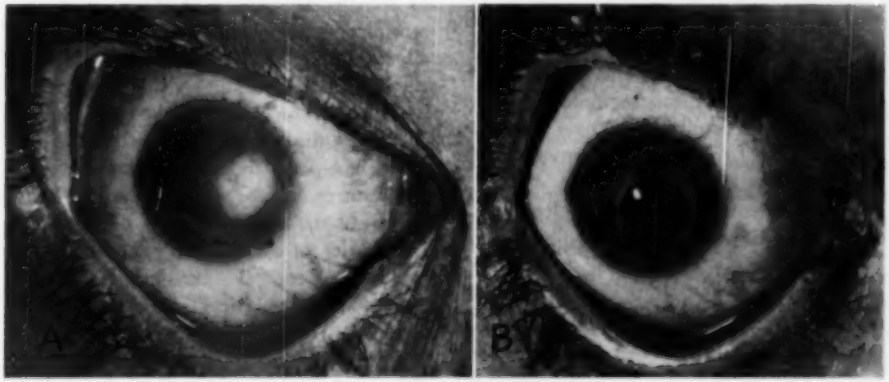

Fig. 9 (Paton). (A) *Adherent leukoma.* Optical iridectomy did not improve the condition. (B) Two months after a penetrating corneal grafting operation.

REMARKS ON THE TECHNIQUE OF CORNEAL TRANSPLANTATION*

TUDOR THOMAS, M.D.
Cardiff, Wales

It was in London (1930) at the 50th annual meeting of the Ophthalmological Society that I first showed clear corneal grafts in rabbits. At that time, it was quite a unique demonstration. About four years later (1934), I succeeded in obtaining, experimentally in rabbits, a clear corneal graft taken from a rabbit 24 hours after the death of the animal.

FIXATION OF THE GRAFT

In the beginning, I found that suturing a rectangular or square graft frequently created a line of tension on the graft, which meant that, after a little while, one of the sutures would come out. The next step was to use overlying sutures, beginning with two parallel sutures coming down over the graft. In rabbits, that resulted almost invariably in the graft slipping out sideways.

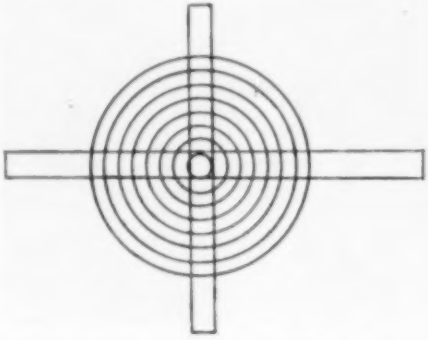

Fig. 1 (Thomas). Sutures placed at right angles.

Two such sutures, at right angles to each other, were then tried (fig. 1). The method is similar to the one now used. Although these sutures retained the graft in place, one of the suture lines would often work to the edge of the graft and would sometimes interfere with its union.

I then carried out two experiments. A razor blade was used to take a shaving from a rabbit cornea and the shaving was replaced with an autogenous graft, without any suturing at all. The graft was simply held in position for a moment. It was left in place, a drop of oil was put on, and the rabbit was returned to its cage. Surprisingly, four out of seven of these grafts took. Four out of seven remained in place, and one of them actually became clear.

It seemed to me that this indicated that there was something to be said for increasing the area of apposition of the margin of the graft and the margin of the recipient cornea. In other words, it seemed to indicate the adoption of some kind of shelving margin. That is what I did.

You are all familiar with the suturing method used at the time I showed clear corneal grafts in rabbits at London (1930). The corneal graft was cross sutured in the ordinary way, the knot being right in the center of the graft (fig. 2). Although I do not recommend the method now—and it has been altered and improved upon—it did give very efficient fixation of the graft. I referred to it, and still refer to it, as eight-point fixation, describing the number of points at the margin. Eight-point fixation can be done with two sutures, or a simple continuous suture may be used.

In order to explain the next step in the evolution of corneal suturing, it is necessary to digress into a paragraph or two of explanation.

When trephines of equal size were used, there was a tendency for the margin of the graft to override a little; it tended to imbibe

* DR. PATON: In introducing Mr. Tudor Thomas, I should like to mention the fact that it was through his early experimental work that I first became interested in corneal transplantation, and it is his technique that I have employed from the very beginning, namely, the trephine method, with some modifications.

secretions, become infiltrated, and produce opacity. In order to produce a snug fit of the graft in the hole—a cork, so to speak, into a bottle—the graft was made somewhat smaller.

At first, the difference in size was about one third of a millimeter. In stages it has been reduced—to a difference of 0.25 mm., then to 0.2 mm. These small differences are quite appreciable.

The suturing modification which followed was to do away with the knot in the center of the graft and to place it in the intracorneal portion at the side. This took the knot

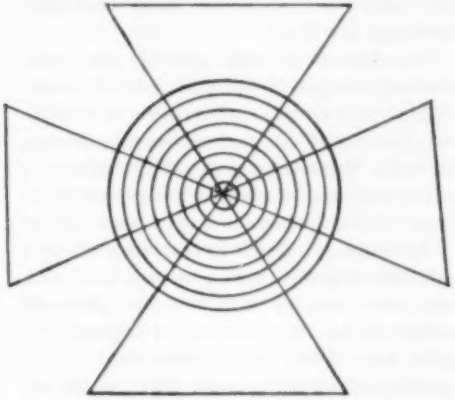

Fig. 2 (Thomas). Diagram of eight-point fixation of the graft.

completely away from the graft, which was quite desirable.

The technique that I still use involves the principle of cross sutures and shelving margins, and the use of trephines slightly different in size. Cross sutures have, on the whole, been rather generally accepted. Concerning these cross sutures and the eight-point fixation, I should like to emphasize one thing:

We are dealing with a science of exactness in which neatness and attention to detail are important. It is essential to obtain exact symmetry in the suturing. The sutures can be inserted accurately and with perfect symmetry but, if one needs a little help, it is not difficult to mark certain points on the cornea with a dye or ink.

Figure 3 demonstrates the technique I now use for placing cross sutures. Point A is marked on the cornea and then point B is marked exactly opposite it. Immediately halfway between points A and B, are indi-

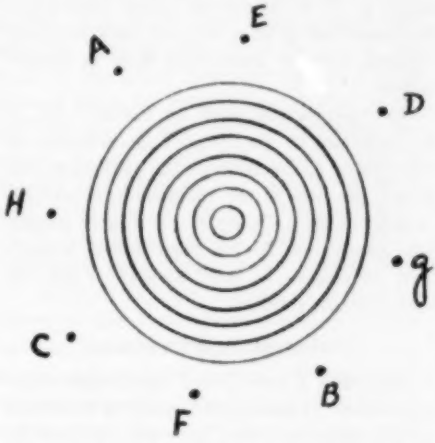

Fig. 3 (Thomas). Diagram of technique used in placing cross sutures.

cated the points C and D. Each of these divisions is subdivided into two exactly equal parts (fig. 3).

Suturing is started halfway between points A and E (fig. 3). Take the suture into the cornea at A, come right across the center to a point midway between B and F. It may be difficult, especially if the needle is a bit curved, to go from A to midway between B and F without penetrating the anterior chamber or coming out through the epithelium. If it is, do it in two bites: a little bite at B, then it runs on the surface of the cornea, then a little bite, and carry out at F. Back across the center to E, passing intracorneally halfway to A. The remainder of the suturing follows this pattern.

If this technique is followed, the sutures will be placed symmetrically and the margin of the graft will be supported equally at the various points. I still use trephines, slightly different in size, and scissors, and a slight shelving margin, with good results and clear grafts.

Prevention of clots

Most operators have, at one time or another, been troubled with fibrinous clots. These may be prevented by using a solution of 30 cc. of sodium citrate (three percent) to 70 cc. of normal saline. Grafts can be immersed in this solution with no more damage than by immersing them in normal saline.

In experimental work on rabbits' eyes, it is important to use some of this solution on everything connected with the operation—the graft, the hole in the recipient eye, and the suture, as well. Doing this will save trouble and annoyance. As has been shown, heparin can, of course, be used instead of this sodium-citrate solution.

Averting complications

Although I have heard the complications of anterior synechias and cataracts discussed, in my experience they have not occurred. In one case, in an unruly patient, a nervous complication occurring a little while after operation did produce an anterior synechia.

Most of the corneal transplantations which I have done have been in cases that would generally be considered unfavorable, with opacities and completely white corneas. If the anterior chamber is normal and there are no unfavorable external conditions, clear grafts can be obtained. In my cases of this kind, 41 percent of the grafts were transparent.

What influences, what principles of technique produce these results? I ask these questions. I do not have the answers. For further consideration, I should like to put forth some points and, since I am not prepared to give the answers, I should like to phrase these points in the form of questions.

Are these complications averted because:

1. The anterior chamber is entered in a shelving manner, with the trephine sloping, and is, therefore, opened more cautiously and damage does not occur?

2. Does the fact that I, personally, like a plain tubular type of trephine, with a maximum view of the cutting point unbroken by any overriding edge, have any influence?

3. Does the use of sodium-citrate in saline solution and the consequent reduction of fibrin formation play any part?

4. Is it because there is no aqueous leak? (With a shelving margin and complete apposition of the two margins with firm pressure by the overlying sutures, there is a watertight joint.)

5. Could it be that in corneal transplantation, I rely on sutures? No pad, but a Cartella shield, is placed on the eye. A dressing is placed on the other eye. After the sutures are removed—in seven days—binocular dressings are used.

It occurs to me that possibly the wide shelving margin of the graft affords better nourishment than is present after a vertical cut, particularly if the surrounding cornea is badly damaged. It would seem worthwhile, perhaps, to consider this especially in cases of very extensive leukomatous scars.

To mention briefly the entrance of vessels into a graft from a vascularized cornea—this certainly need not take place. It seems to me that such an occurrence implies some defect in the graft itself—some nutritional defect, or some defect in the fit, or some overriding of a part of the margin.

The tendency of vessels to invade the graft depends, as you know, on damaged rather than on destroyed cells. If cells are destroyed—if a piece of cornea is boiled in oil and transplanted, it can be made to unite and remain in place. No vascularization takes place. There is no irritation. However, if the cornea is burned, either grafted or otherwise, it is quite a different matter.

Fate of grafted tissue

From my own experience and speaking only from my own observations, it seems to me that this is what happens to grafted tissue. In the course of time, in the ordinary homogenous graft, the epithelium is replaced; the graft's own Bowman's membrane remains; the graft stroma remains, subject to any physical change that normally

takes place in the cells; the graft's Descemet's membrane remains although the endothelium (here I am uncertain) is probably replaced in the course of time and, later, a new Descemet's membrane is formed.

Experimentally, I have observed another type of graft—that is, transplantation of the sclera to the cornea, with the graft taken from the sclerotic membrane rather than from the cornea. In the course of time, say after the second year, the results seem to show that the graft consists of epithelium and endothelium, derived from the tissues of the recipient eye, and a stroma which contains the remains of the posterior fibers of the graft with new fibers from the host developing in situ. These fibers also come from the corneal cells and migrating cells.

Some of the posterior fibers in the scleral graft are derived from endothelium and, in a vascularized graft, a great many are laid down by the vascularized tissue itself. At the end of two years, the scleral graft has a well-formed posterior elastic membrane, which is, of course, a new formation, formed from the endothelium.

Heterogenous grafts can unite, but invariably, become vascularized. Usually in a heterogenous graft, say cat to rabbit, primary union is incomplete, and there is a good deal of breaking down of the tissue of the graft itself, surface disintegration, so that the epithelium which is present after a time is obviously replaced from the tissues of the host. This commences in less than two weeks and is complete in much less than two months.

Underneath the epithelium there is a subepithelial layer of fibers with vascularized tissue, derived from the recipient corneal stroma, and these fibers grow around and into the heterogenous graft fibers. At the back of the graft there are layers of cells derived from the endothelium of the recipient eye, and a new elastic membrane develops, to my knowledge, in less than 14 months and more than 3 months. After a year to 18 months, these findings are present in the graft tissue: epithelium and a substantial subepithelial layer derived from the recipient eye; the original, broken-down fibers of the heterogenous graft; another layer of fibers, with a posterior elastic membrane and endothelium—all derived from the recipient eye. This picture of a subepithelial layer, the other layers at the back, and an endothelial layer, with the broken-down remains of the graft in the middle, gives one the impression of tissue which is tolerated but ostracized by the recipient eye. The host will take the heterogenous graft; it will surround it; and it will shut it off as much as possible. To emphasize: If a section is cut through a heterogenous graft and an adherent iris, it is almost certain to show that the iris is growing into the cornea of the host rather than into the tissues of the graft.

Discussion

Question 1

Do you dilate or constrict the pupil before surgery?

Mr. Tudor Thomas (Cardiff, Wales): I always dilate the pupil before operating. I started that technique in rabbits; I have continued it in man. I do not regret it because I have never encountered cataract as a postsurgical complication. I suppose the main purpose in constricting the pupil before operation is to prevent damage to the lens. However, it might be that dilatation favors the prevention of iris adhesions. I always dilate the pupil before operation.

Question 2

How do you obtain the bevel in your technique?

Mr. Thomas: First, I use the trephine in a vertical position and then I tilt it a little, going in at one side. When taking a graft, I go fairly deep vertically, then open boldly

on one side, and continue with scissors around the graft, holding the scissors in a slightly sloping position.

In opening an opaque cornea, one has to be very careful, for in opaque corneas there are differences in thickness. The vertical incision is not quite so deep. As soon as I feel that I am into the stroma of the cornea, I tilt the trephine and open the incision obliquely. On the least sign of aqueous, I take the trephine out.

If the opening is not large enough to introduce the tip of a scissors, I increase it very slightly.

REMARKS ON THE TECHNIQUE OF CORNEAL TRANSPLANTATION

MAUNO VANNAS, M.D.
Helsinki, Finland

The greater number of my transplantations are already more than 10 years old; so also are most of the following observations published in 1939 and later confirmed.

To make a pentagonal graft, in order to get the angles wider than they are in a square, I have a metal stamp, similar to a rubber stamp, consisting of needles. A slight pressure with this stamp and the needles bite into the surface of the cornea making small marks in the epithelium. A drop of fluorescein on the cornea makes these marks visible.

It is very easy then to cut along these lines for a pentagonal graft, which I like because it has wider angles than the square graft. However, I prefer the round graft, as you do. Contrary to the practice of other operators, I commonly use a mechanically driven trephine. With this high-speed trephine, I obtain a completely isolated transplant, not only from the donor but even from the recipient cornea in almost 10 percent of the cases. If I need scissors, I have to cut only a very short distance at the periphery.

It would seem reasonable to ask: "How often is the lens or iris injured with such a method?"

There is a preventive method needed, and I always use it if the anterior chamber is even a little more shallow than normal. This preventive method consists of the injection of 10 percent, now commonly 20 percent, gelatine solution into the anterior chamber before the grafting. The injection is done with my needle which has a hole on the side, as is shown in Blascovics's *Surgery*. The gelatine keeps the anterior chamber deep, then it slowly comes out through the trephine hole, and the rest of it disappears from the anterior chamber in a few hours.

To keep the transplant in place, I use no threads on the graft but a very thin rubber membrane. The thinnest and strongest rubber membrane in the world is the condom rubber. It is also transparent and suitably flexible.

The sutures are placed in the usual way (before trephination) at the limbus or as near the graft as you want. The rubber is conveniently cut between two papers of the correct size and sutured with four, five, or more sutures, almost as the cornea is sutured in the cataract operation. Two or three of the upper sutures have already been tied before the trephination. Consequently, the graft is put, as it were, under an updrawn curtain, which then will cover the transplant, its lower margin being sutured.

The larger the graft, the more advantageous, I believe, is the rubber membrane.

Almost 30 percent of my grafts are from stillborn children, because to date that has been my most available material. I have the impression that it is as good as the other materials. One of my best patients, operated on at the age of 15 years, has stillborn material. Now, after 12 years, the vision is still normal.

There is, however, a disadvantage in using these children's corneas. The small size, especially the short radius of curvature of the stillborn cornea, makes the patients highly myopic. Therefore, only a contact glass can help these patients. So, the patient has normal vision with a contact glass, but vision of not more than 0.1 with the best possible correction with spectacles.

In conclusion, I should like to ask: Will you shortly have the courage to begin to correct refractive errors with corneal grafting?

The natural way for increasing the refraction would be to substitute the children's eyes with a graft of greater curvature than the cornea, and there is certainly the possibility of finding a way to decrease the refraction.

DISCUSSION

QUESTION 1

Do you put the rubber membrane on a stretch when you suture it in place?

DR. VANNAS: I put in two or three sutures first. I don't know whether it is better to put them in the direction of the radius or anteriorly and then twist them through the rubber membrane. I have tried both.

If the transplant is very large, then I put my sutures at the limbus. These sutures are then put through the rubber membrane and definitely tied. They are ready there, and the membrane is hanging over the cornea as a curtain. The trephining is done under the membrane. As the transplant is placed into position, the curtain is lowered. The sutures are ready and tied. If additional sutures are needed—and you have good needles—it is possible to put them in.

ROUND-TABLE DISCUSSION

DAVID H. WEBSTER, M.D., *Chairman*
New York

QUESTION 1

Why do French surgeons use grafts of a different size from the recipient bed?

DR. G. P. SOURDILLE (Nantes, France): To answer that question is difficult because it is to tell the whole story of the graft. At first everyone used the same size for the host and the donor.

Franceschetti was, I believe, the first one to use trephines of different size for the graft and the recipient cornea. He did this, it seems to me, because he had lost a graft which fell into the depths of the anterior chamber. He constructed trephines with a difference of 0.1 mm. and used the larger one for the graft. Now, I think, for the penetrating graft, everyone uses the larger for the host and the smaller for the graft.

It is interesting to follow the various stages in the evolution of this problem. While Mr. Thomas was speaking of beveling the incision, it occurred to me that, in the beginning, all of us were afraid that the graft would fall into the anterior chamber.

I now use a slightly beveled incision, but different in size from that used by Mr. Thomas. I think it is more important to have a slightly larger cut in Descemet's membrane than in the anterior layers of the cornea. Scars are very frequent when the cutting of Descemet's membrane is not well done. In many cases, a good incision of Descemet's membrane is not made with the trephine. That is easy to understand. When pressure is applied to the trephine, the curvature of the posterior layer of the cornea is modified, and there is a difference between the anterior and posterior radius. For this reason the use of different trephines is im-

portant. When I use the same trephine, a conical deformity of the graft more frequently results.

QUESTION 2

Should the cornea be entirely free from new blood vessel formation before any type of corneal surgery is attempted?

MR. TUDOR THOMAS (Cardiff, Wales): I think I might venture to answer that question in this way: In interstitial keratitis you can get quite nice results although there are blood vessels in the cornea.

DR. SOURDILLE: If a lamellar keratoplasty is done, it is not harmful to have blood vessels. I have operated on cases in the beginning of the second period of Hutchinson's keratitis, during the penetration of the vessels into the cornea. It is amazing to see how the corneal lamellar graft can stop the penetration of the vessels in this stage of the disease.

QUESTION 3

How can postoperative myopia and astigmatism be prevented?

DR. JOHN MCLEAN (New York): I wish I knew the answer. However, I do not believe it is of great importance because a patient whose vision is so poor that he requires a corneal transplantation will not be concerned about whether or not he is going to have to wear glasses. From time to time, contact lenses may be required to give maximum visual acuity.

QUESTION 4

Discuss postoperative pressure in corneal transplantation for keratoconus.

DR. BRENDAN D. LEAHEY (Lowell, Massachusetts): Usually, unless there is some late bulging of the graft, postoperative pressure is not used in cases of keratoconus. In cases other than keratoconus, pressure is used when there is actual bulging of the graft.

Recently, I had a case that worried me a great deal. It was a cross section, and the graft bulged all around. The patient had a secondary glaucoma. The graft came up with the trap door which was poorly set in. Miotics were administered and pressure was applied for about 10 days. The graft became perfectly all right and is clear at the present time.

Some surgeons, however, routinely advise pressure in the keratoconus cases, starting about three weeks after operation.

QUESTION 5

Is there any correlation between the speed of epithelial regeneration over the graft and the absence of postoperative edema of the graft?

DR. LOUIS PAUFIQUE (Lyon, France): There is no correlation, as far as I know. The regeneration is too rapid to have any relationship with the destruction of the epithelium. The most important part is the posterior surface. When the graft is deep in the anterior chamber, aqueous fluid seeps into the deepest layers, and I think that is much more important than the epithelium. The epithelium is not so very important.

QUESTION 6

What effect does the local application of sulfonamides have on the healing of corneal wounds—that is, how does it affect cellular migration and mitosis of the epithelium?

DR. WILHELM BUSCHKE (New York): There have been some studies on the effect of various sulfa drugs on both migration and mitosis. However, the results were not quite consistent in that the inhibitor effect produced on mitotic activity in the epithelium by some of the sulfa drugs did not seem to be due actually to the sulfa drug but rather to the size and distribution of particles in the ointment which had been applied. The particles, which have a somewhat mechanical damaging effect, would produce an inhibition of mitosis. There would seem to be no damaging or detrimental effect on either the

movement of cells or the mitotic activity due to sulfa drugs in therapeutic doses.

QUESTION 7

Is it safe to use eyes with malignant tumors for donor material?

DR. PAUFIQUE: One case in which retinoblastoma was transferred from the donor to the host has been reported by a Japanese surgeon. If a donor eye is affected with reintoblastoma, I do not use the eye.

DR. SVEN LARSSON (Lund, Sweden): We had a case at the Infirmary about a year ago of a ring sarcoma with pigment deposits in the back of the cornea and uveitis. Dr. Verhoeff saw this eye and he advised against using it because, as he said, some of that pigment might grow in the new eye. There has been no case reported of its happening, but he felt it was probable that it might happen in this case.

DR. SOURDILLE: This may not be the occasion to say this: but I think the grafting operation is not so dangerous. Last year I operated on a case using a graft coming from an eye which had been eviscerated from a friend of mine. I could not obtain another donor at the time. Three days afterward, the second eye was affected with sympathetic ophthalmia, and I was very worried for 20 to 30 days as to the outcome. We nursed the case along and the result turned out to be good.

MR. THOMAS: Mr. Chairman, might I suggest that this is a very important question and I think we out to answer definitely that the risk is either nil or negligible? I, like Dr. Paufique, have heard of only one case, and that was the Japanese case in which a glioma was transferred. I have used a fair number of eyes with melanotic sarcomas and a few—a much smaller number—with gliomas, and I have never had such occurrence.

As we have gathered together here those who are interested in corneal transplantation from a wide section of the globe, the whole of America, and parts of Canada, I believe that if there is anyone here who has had experience with such a thing that we should hear it now; and if there isn't we will know that we are on safe ground.

DR. PAUFIQUE: I can say one thing: Emery, who was a very good corneal surgeon, used only fresh eyes removed from patients in his clinic. He used melanosarcomatous eyes and he never had a complication. But with retinoblastoma you do not have the same situation.

DR. PATON: I am glad Mr. Thomas emphasized the importance of this. Serious trouble could result if there were any disagreement.

The Eye-Bank is taking the stand that the surgeon who uses the eye knows, of course, why the eye was removed and he, of course, is finally responsible if anything goes wrong with the patient. We are not, however, advising or recommending the use of gliomatous eyes, particularly as some of these eyes show precipitates on the back of the cornea, and there might be tumor cells present. Although the Japanese case is the first and only one I have ever heard of, we have advised against the use of gliomatous eyes just because there may be some doubt in some cases.

DR. DAVID FREEMAN (New Haven, Connecticut): I should like to say one word about the carrying over of retinoblastoma. I personally doubt that occurrence very much, for two reasons: First, among numerous cases, only one instance has been reported and that in a very distant country. There is a great difference of opinion many times as to the diagnosis on the section. The second reason is that, in the laboratory in which I work, Dr. Green, who has grown most human tumors, has been unable to grow any nerve-originating tumors.

DR. MCLEAN: I wonder if Dr. Green has tried many retinoblastomas.

DR. FREEMAN: We have tried one, because we have just become interested in that, and have found, for three to four months up to the present time, that there has been no

growth with a freshly removed retinoblastoma.

DR. KATZIN: I assume that the retinoblastoma was transplanted into an animal.

DR. FREEMAN: Yes, a lower animal. We do not use human beings.

DR. DEVOE: I asked Dr. Levine that same question. His answer was that nobody would ever do it to his eye. So, I don't know. He seemed to be quite doubtful about it.

DR. FREEMAN: Of course, we are not transplanting these to human beings. We have tried several types of animals that readily grow all carcinomas, but with the nerve-tissue tumors there has never been any growth.

DR. I. M. GREEN: I recently had an opportunity to study a large number of eyes with some metastatic carcinoma, and in those eyes you do find cells precipitating on the posterior surface of the cornea. Since they are transmissible, I think a point to be borne in mind is that these eyes probably should not be used. I feel as Dr. Devoe stated: I would not want them used on me.

DR. CHARLES ILIFF (Baltimore): I think it is important to divide the two types of tumors implied in the question, (1) retinoblastoma and (2) melanoma, because retinoblastomas, of course, are seen in all the tissues of the eye and extend locally; whereas, the melanomas very rarely metastasize to other portions of the eyes and, if they do, it is late. In the retinoblastomas, however, it is very early. I think that would make a difference in consideration of the question.

DR. LEAHEY: I should also like to suggest that the melanomas should be divided as to whether they are anterior or posterior. We have done a number of cases with posterior melanomas. Some of them have gone 10 or 11 years without recurrence. We never thought of the possibility that there could be recurrence.

In the case I mentioned we actually found deposits on the back of the cornea. We know they are transmissible. The anterior chamber is a beautiful place to grow tumors, so that is the reason I would advise against using that kind of a graft when there is an anterior tumor, a ring sarcoma with proliferation of pigment on the cornea and in the angle and a few pigment spots on the back of the cornea elsewhere.

DR. JOSEPH LAVAL (New York): I think Dr. Paton has summed the question up rather concisely. If the physician who is going to graft the cornea knows the eye of the donor, as Dr. Paufique mentioned—in some clinics each donor's eye is examined by the surgeon—then he can be safe. He will know whether the retinoblastoma has involved the cornea; he will know whether the sarcoma is posterior or anterior. But we in the Eye Bank, as Dr. Paton said, have to be extremely careful because we don't see these eyes until they are brought to us in bottles. Therefore, I think Dr. Paton is right that we should not give away eyes for transplant that harbor retinoblastoma or that harbor sarcoma anterior to the equator.

DR. FREEMAN: How can the surgeon be sure that the growth is anterior or posterior when there can be seeding of invisible cell elements all over?

DR. LAVAL: All the sarcomatous and retinoblastomatous eyes that are examined in the laboratory here, for example, don't show microscopically any seeding anteriorly unless those seedings have been visible with the slitlamp. If you don't see any with the slitlamp, you won't see any with the microscope in the laboratory. If the surgeon examines the gliomatous eyes clinically with the slitlamp, he will know whether there are seedings, and he will certainly know clinically from the sarcomatous eyes whether the lesion is in the choroid or is in the anterior portion near the ciliary body. If he is not certain, he should not use the eye.

DR. PAUFIQUE: I think it is best not to use the eye of a patient when it is known that there is a tumor. It is better to wait and use a good eye.

QUESTION 8

Is it safe to use a transplant from a donor who has not had a Wassermann test?

DR. MCLEAN: I think that question nearly parallels the tumor question.

It is, in all probability, impossible to transmit syphilis through a piece of cornea. Nevertheless, I feel sufficiently unsure, and I should like to know that the donor patient did not have syphilis before using that as a donor eye. It is an experiment which, to my knowledge, has never been performed, and I am not anxious to be the first one to perform it and get a positive result on a patient. It is probably safe, but there is a possibility that it is not.

DR. LAVAL: I should like to ask a question. Can syphilis be transmitted in avascular tissue? Does anybody here know?

DR. ILIFF: To answer your question indirectly: there have been only two or three proved cases in which spirochetes were actually found in the cornea, and those were cases that had an actual keratitis. A cornea that does have a keratitis present would not be transplanted so I think it is very doubtful that any organisms would be transplanted.

DR. MCLEAN: It is doubtful, but can you prove it?

QUESTION 9

In a highly vascularized cornea should a keratectomy be done before or after irradiation?

DR. LEAHEY: In a few cases in which the radium-D applicator has been used, the procedure has been to do a keratectomy first if the lesion is large enough and follow this with beta irradiation. If there is a large blood vessel trunk, not enough to do a stripping on, the irradiation treatment is given first, and, at the same time or right after, a peritomy is done. Other irradiation treatments follow. Two or three drops of pontocaine are used for anesthesia.

QUESTION 10

Will Dr. Wiener mention any advantages of his corneal punch over the trephine?

DR. MEYER WIENER (Coronado, California): I think it has many advantages. First of all, it is almost impossible to injure the lens. Secondly, it gives a beveled edge which prevents the cornea from slipping in and gives a wider adhesive surface. Again, since the two surfaces are maintained mechanically, both the donor and recipient grafts are identical, which I think is very important.

I retired 13 years ago and I have not done any of these myself. Only my students have done them, and there have not been many done. But the reports that I get seem to be most favorable and they become more favorable from time to time. We did have difficulty in getting the anterior synechias. We used to do a complete iridectomy. Since using the McLean sutures for a keratotomy incision and doing an iridotomy and then injecting air into the anterior chamber after the operation was complete, we have not had any anterior synechias.

One more reason why it is advantageous to use the punch: It is very easy. It takes only about 12 minutes to do the operation.

QUESTION 11

What is the benefit of decompression after lamellar graft if the anterior chamber refills in a few minutes?

DR. PAUFIQUE: At the end of a lamellar graft, I refer to a partial lamellar graft only, you can see that the posterior layers of the cornea are very thin, and that the pressure of the anterior chamber pushed them out. Consequently, it is not easy to put the graft in place.

However, I open the anterior chamber at the end of the operation. The fluid does come again, but during this time the adherence of the graft to the cornea is very rapid. It is very useful to open the anterior chamber after a partial lamellar graft in order to get a good placement of the graft.

MR. THOMAS: May I follow that with another question to Dr. Paufique?

In a perforating graft, the adhesion would have to be entirely between the graft and the cornea. Do you find it adheres quickly enough to effect this?

DR. PAUFIQUE: Oh, yes, after the opening of the anterior chamber.

QUESTION 12

Why do the European doctors use eserine after the graft?

DR. SOURDILLE: In some cases we use atropine; in some cases we use eserine. That is easy to understand. When you use a 5.0-mm. graft, you can dilate the pupil readily, and beyond the graft there is no more iris. When you use a 6.0- or 7.0-mm. graft, you cannot hope to open the pupil widely enough. The border of the sphincter is beyond the graft. In such conditions I think it is better to use eserine for the first dressing. And it is the same situation when you have a previous iridectomy. You cannot dilate the pupil sufficiently if you use a large graft.

DR. LAVAL: Do you think that with neosynephrin you might open the pupil widely enough?

DR. SOURDILLE: I use neosynephrin (two percent) very often.

DR. LAVAL: Then you would not have to use eserine?

DR. SOURDILLE: With a 6.0- or 7.0-mm. graft neosynephrin is not sufficient, because its action is not long enough.

QUESTION 13

Will Dr. Kronfeld give some of his experiences with control of secondary glaucoma medically and surgically in postoperative corneal transplant cases?

DR. PETER C. KRONFELD (Chicago): My experience with glaucoma following corneal transplantation is very limited, but I believe that most of these are cases due to proliferating anterior synechias as a result of the presence of a shallow chamber or absence of a chamber.

The surgical procedure that I have had to use a few times and that I would recommend is cyclodialysis with a spatula in the anterior chamber; in other words the operation that Dr. Paul Chandler in Boston advocates for elderly people. I would do a cyclodialysis from both sides, permitting the tip of the spatula barely to appear in the anterior chamber—pushing in a forward direction then back and sideward, breaking all the synechias posteriorly and forward.

I have done a few of those cyclodialyses, and they have worked just as well as cyclodialysis works in other cases. A comparable situation would be in glaucoma following cataract operation with absent chamber.

With regard to the medical treatment of these cases, I believe that the eserine cases do proportionally better than the proponal group or the acetylcholine group. I know of three cases in Chicago that are quite well controlled with small amounts of eserine. One case does quite well on D.F.P.

On the whole, however, glaucoma secondary to corneal transplantation is a rare condition, especially with the improvement in technique.

I had to acquire the technique for doing corneal transplants in China, and I know very little about it. But there the incidence of secondary glaucoma was small.

Once a glaucoma has established itself and does not respond to the first cyclodialysis, I think the chances of success with the second cyclodialysis are very small. Instead of doing a second one, I would prefer to do a cyclodiathermy.

QUESTION 14

Can the eye of a patient who has died of scarlet fever or any infectious disease be used for donor material?

DR. KATZIN: No.

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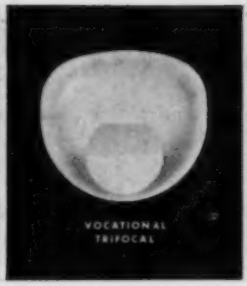

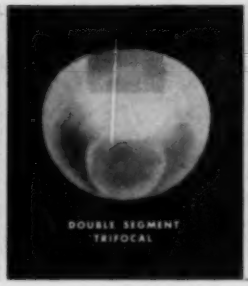

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